Chasing Time: The Specific Impacts and Dynamic Relationships of Physical Activity, Sedentary Behaviour, and Sleep on Older Adults’ Cognitive Health

by

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Abstract

Effective lifestyle and behavioural strategies which maintain the cognitive health of older adults with Mild Cognitive Impairment (MCI) – a transition stage between healthy cognition and dementia – are greatly needed. There are three time-use activity behaviours which all humans engage in daily: physical activity (PA), sedentary behaviour (SB), and sleep. Each time-use activity behaviour is linked to cognitive health, although the magnitude of these relationships are still uncertain. There is also preliminary evidence that these time-use activity behaviours share a complex and dynamic relationship with each other and cognitive health. Thus, the aim of this dissertation was two-fold: 1) to advance the current knowledge about the dynamic relationships between time-use activity behaviours and cognitive health; and 2) to characterize potential time-use activity behaviour intervention strategies for promoting cognitive health. Using a systematic review of observational studies, I showed SB is associated with poorer cognitive function. I next conducted three cross-sectional studies which found 1) the relationships of PA and SB with cognitive function differ by MCI status; 2) PA is associated with better cognitive function independent of any sleep index, while only sleep efficiency is associated with cognitive performance independent of PA; and 3) PA is associated with greater brain cortical thickness independent of SB, but SB is not associated with cortical thickness independent of PA. I then conducted a secondary analysis of a randomized controlled trial (RCT), where I found that while the intervention significantly increased older adult PA, it did not improve cognitive function. My final thesis study was a proof-of-concept RCT to examine the effects of multimodal chronotherapy to promote better sleep among older adults with MCI and poor sleep; I found the intervention improved subjective sleep, but did not improve objective sleep or cognitive function. The results of my thesis contribute to a better understanding of how time-use activity behaviours impact older
adult cognitive health, and helps to refine the public health message for best promoting healthy
cognitive aging through lifestyle.
Lay Summary

Effective behavioural strategies to promote healthy cognitive aging are greatly needed. Three behaviours related to cognitive health which all adults engage in daily are: physical activity (PA), sedentary behaviour (SB), and sleep. My thesis examined how PA, SB, and sleep are dynamically related to each other and cognitive health. I found: 1) SB is associated with poorer cognition; 2) the relationships of PA and SB with cognition vary by cognitive status; 3) PA and sleep are each independently associated with cognition; 4) PA is associated with better brain structure independent of SB, but SB is not associated with brain structure; 5) increasing PA does not improve cognition in highly active community-dwelling older adults; and 6) a multimodal lifestyle intervention improves sleep but not cognition in older adults at risk for dementia. My thesis contributes to a better understanding of how PA, SB, and sleep impact older adult cognitive health.
Preface

Content from this dissertation was written and compiled (for the published chapters) by Ryan Stanley Falck. Professor Teresa Liu-Ambrose, Professor Todd C. Handy, Professor Karim Khan, and Professor Jennifer C. Davis provided comments that were taken into consideration in generating the final version of the dissertation.

The research studies in Chapters 2-7 were primarily conducted in the Aging, Mobility, and Cognitive Neuroscience Laboratory at the Research Pavilion of the Vancouver General Hospital. All magnetic resonance imaging was conducted at the UBC MRI Research Centre. Ethics approval for all studies was approved by Univeristy of British Columbia’s Clinical Research Ethics Board (H14-01301; H14-01762; H16-01029). All research presented in this thesis has been published or is submitted for publication. Details for each publication is provided below.

Chapter 2 is based on work conducted in the Aging, Mobility, and Cognitive Neuroscience Laboratory by Ryan Stanley Falck, Professor Jennifer C. Davis (supervisory committee member), and Professor Teresa Liu-Ambrose (supervisor). I was responsible for writing the first draft of the manuscript, performing the search strategy, reviewing the articles, and drafting the tables. Professor Davis provided help with the article reviews and drafting tables. Professor Liu-Ambrose and Professor Davis conceived the study concept and design, and wrote portions of the manuscript and provided critical review of the manuscript. All authors approved of the final manuscript. A version of Chapter 2 has been published:


Chapter 3 is based on work conducted in the Aging, Mobility, and Cognitive Neuroscience Laboratory by Ryan Stanley Falck, Dr. Glenn J. Landry, Dr. John R. Best, Professor Jennifer C. Davis, Mr. Bryan K. Chiu, and Professor Teresa Liu-Ambrose. Dr. Best, Dr. Landry, Professor Davis, Professor Liu-Ambrose, and I were each responsible for the concept and research design of the study. I wrote the first draft of the manuscript and performed all statistical analyses, and received critical review of the manuscript from Dr. Best, Professor Davis, Mr. Chiu, and Professor Liu-Ambrose. All authors approved of the final manuscript. A version of Chapter 3 has been published:


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I wrote the first draft of the manuscript and performed all statistical analyses, and received critical review of the manuscript from Dr. Best, Professor Davis, and Professor Liu-Ambrose. All authors approved of the final manuscript. A version of Chapter 4 has been published:


**Chapter 5** is based on work conducted in collaboration between the Aging, Mobility, and Cognitive Neuroscience Laboratory and the Arthritis Research Centre by Ryan Stanley Falck, Dr. Chun Liang Hsu, Dr. John R. Best, Professor Linda C. Li, Dr. Anna R. Egbert, and Professor Teresa Liu-Ambrose. Dr. Best, Professor Liu-Ambrose, and I conceived the study concept and design. Dr. Best and I collected the data. Dr.’s Hsu and Egbert and I performed the data analyses and interpreted the results. I wrote the first draft of the manuscript, and Dr.’s Best, Hsu, and Egbert, and Professor’s Li and Liu-Ambrose wrote portions of the manuscript and provided critical review. All authors approved of the final manuscript. A version of Chapter 5 is accepted for publication in *Medicine and Science in Sports and Exercise*.

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Dedication

To Joyce B. Thorsten and Audrey Falck, my grandmothers who each passed away shortly before I finished this thesis. I hope to age as well and enjoy life as much as they both did.
Chapter 1: Introduction

1.1 Preamble

Worldwide, one new case of dementia is detected every four seconds [1]. Given the world’s aging population, the lack of effective drug therapy, and the fact a cure for dementia is likely many years away – there is an urgent need to develop interventions to prevent or at least delay dementia’s progression [2]. The societal value of identifying and developing effective behavioural strategies to help reduce dementia risk is thus an important line of scientific inquiry.

Broadly, there are three time-use activity behaviours which all humans engage in daily: physical activity (PA), sedentary behaviour (SB), and sleep [3]. Current evidence suggests PA is one important and modifiable lifestyle behaviour which can have substantial effects on older adult cognitive health [4, 5]. Emerging evidence also suggests SB is associated with poorer cognitive health [6, 7]. SB is a distinct behaviour from PA and may have different effects on cognitive health [8]. There is also a growing body of evidence which indicates poor sleep is a risk factor for cognitive decline and dementia [9]. Promoting increased PA, reduced SB, and better sleep may thus each have important benefits on older adult cognitive health.

Each of these behaviours also share a complex and dynamic relationship with each other and cognitive health [4]. Although PA and SB are independent behaviours, greater amounts of SB are consistently linked to lower PA level, and vice-versa [10]. PA has also long been thought to improve poor sleep [4], and people that are more physically active report sleeping better compared with people that are more sedentary [11]. Little is known about the impact of SB on older adult
sleep quality, although given the links between PA and sleep, it is plausible that SB may impact sleep too. Sleep is also inextricably linked to the function of circadian rhythms—the ~24 hour biological clock which helps align the sleep-wake cycle with the solar light-dark cycle [12]. A growing body of evidence suggests that circadian dysregulation is associated with poorer cognitive health and an increased risk of dementia [2]. PA and SB can also act as external stimuli on the biological clock, causing shifts in the timing of the clock, which may alter sleep patterns [4]. Given these complex interrelationships, it is critical to establish how PA, SB, sleep and circadian rhythms can each impact cognitive health—and whether this occurs simultaneously, in synergy, or in silos.

Thus, the overarching goals of my thesis are to: 1) advance the current knowledge about the dynamic relationships between time-use activity behaviours and cognitive health; and 2) characterize potential time-use activity behaviour intervention strategies for promoting cognitive health. This introduction provides the background knowledge and motivation for my thesis studies. Much of this background section is drawn from two book chapters I co-authored [4, 5].

Broadly, I will present this background section in six parts (Sections 1.2 – 1.7). I will first discuss the growing public health challenge of healthy cognitive aging, the definition of cognitive health, and the means by which cognitive health is measured (Section 1.2). In Section 1.3, I will review how PA (Section 1.3.1), SB (Section 1.3.2), and sleep impact older adults’ cognitive health (Section 1.3.3); definitions for each of these terms will be provided, as well as an overview of how each behaviour can be measured.
Section 1.4 will discuss the relationships of time-use activity behaviours with circadian rhythms, as well as the relationships of these behaviours with older adult cognitive health. In order to determine the dynamic relationships of time-use activity behaviours with cognitive health, it is important to measure these behaviours concurrently, and thus I will first discuss methods for the concurrent measurement and analysis of multiple time-use activity behaviours (Section 1.4.1). I will then review the current evidence examining the dynamic associations between time-use activity behaviours and cognitive health (Section 1.4.2), as well as the associations of these behaviours with circadian rhythms (Section 1.4.3).

Current therapies and interventions to promote PA, SB, sleep and circadian regulation will subsequently be discussed in Section 1.5. Lastly, I will review the current gaps in the literature (Section 1.6) and highlight what questions my thesis will address (Section 1.7).

1.2 The cognitive health of older adults: A growing public health challenge

By 2030, there will be nearly one billion older adults worldwide [13]. Because age is the most important non-modifiable risk factor for dementia [14], an exponential increase in the number of individuals with dementia is expected [15]. There is therefore an urgent need for effective strategies which reduce dementia risk or delay disease progression.

Inextricably linked to the number of dementia cases worldwide is the prevalence of cognitive decline among older adults. An estimated 10-20% of adults over 65 years of age are living with Mild Cognitive Impairment (MCI; [16]), a transitional stage between healthy cognition and dementia [17]. MCI is defined as cognitive decline greater than expected for age and education
level which does not interfere with independence [18], and is associated with up to a 30% increased risk of developing dementia within five years [19]. Older adults without MCI develop dementia at a rate of 1-2% within five years [20]. Providing effective strategies to maintain cognitive health before and during this transition period might slow or prevent conversion to dementia. Thus, achieving cognitive health for all older adults is a growing public health priority which requires immediate solutions in order to effectively slow dementia rates [21].

1.2.1 Defining cognitive health

A standardized definition of cognitive health is currently not established [22]. Perhaps the closest to a consensus definition is the one proposed by the National Institutes of Health’s Cognitive and Emotional Health Project [23], which described cognitive health as “not just the absence of cognitive impairment, but the development and preservation of the multi-dimensional cognitive structure that allows the older adult to maintain social connectedness, and ongoing sense of purpose, and the abilities to function independently, to permit functional recovery from illness and injury, and to cope with residual cognitive deficits.” Key elements of this definition are that cognitive health combines multiple domains of cognitive function, including traditional and measurable neuropsychological abilities (such as memory and processing speed), as well as more esoteric constructs such as wisdom and resilience. This definition also considers central the link between cognitive health and functional independence and engagement with life [22].

1.2.1.1 Normal cognitive aging

While it is difficult to concisely define cognitive health at this time, there are specific aspects of cognition that change as people age. Domains of cognitive function which decline with age include: 1) attention; 2) memory; 3) executive function (i.e., planning and problem solving ability
(i.e., reading ability, general knowledge, language, etc.) remain relatively stable over the normal adult lifespan [26].

The normal aging process is also characterized by multifaceted changes in brain structure and function, which results in age-related changes in cognitive function [27]. These continuous, age-related changes begin as early as the third decade of life and include 1) declines in regional brain volume, myelin integrity, and cortical thickness [28]; 2) decreased availability of neurotransmitter receptors (e.g., serotonin or dopamine) in the cortex [29, 30]; 3) accumulation of beta-amyloid (Aβ), neurofibrillary tangles, and other various brain metabolites [31-33]; and 4) changes in brain activation patterns at rest and during performance-based tasks [34, 35].

1.2.1.2 Cognitive changes in Mild Cognitive Impairment and dementia

While some changes in cognition appear to be an unavoidable consequence of the aging process, there are some aspects of cognition which appear (at least on average) to be markedly different in individuals with MCI and dementia compared with their healthy cognitive counterparts [17-19]. Perhaps most obvious among these differences, older adults with MCI and dementia have poorer performance on neuropsychological tests of cognitive function—specifically in the domains of memory and executive function [19, 36, 37]. There also appear to be differences in age-related brain structure and function for individuals with MCI and dementia [38]. For example, compared to older adults without MCI, those with MCI have: 1) greater amounts of Aβ accumulation [39]; 2) accelerated declines in total brain volume, as well as deterioration in volume of the temporal and frontal lobes [40]; and 3) cortical thinning in the medial temporal lobe, and the frontal and parietal regions [41]. Increases in Aβ levels [42], accelerated atrophy in the medial temporal lobe
[43], as well as cortical thinning in the frontal, temporal and parietal lobes [44, 45] are each indicators of Alzheimer’s disease (AD) and dementia.

Older adults with MCI, when compared to their healthy peers, also exhibit disrupted functional connectivity [46], as well as changes in the activation of the temporal lobe, frontal lobe, and limbic area during performance-based tasks [47-50]. Disrupted functional connectivity, as well as altered brain activation of the frontal, temporal and parietal regions during task-based functional neuroimaging tests are each indicators of dementia [51, 52]. Interestingly, there do not appear to be differences in electrical signaling between age-matched healthy older adults and older adults with MCI [53], although changes in electrical activity appear to occur as people transition from MCI to dementia [54].

While people with MCI and dementia appear to have substantial differences compared to their healthy cognitive peers in performance on neuropsychological tests, as well as exhibiting brain structural and functional changes, the exact etiology and disease progression that occurs from healthy cognition, to MCI, to dementia is not clear. For example, autopsy studies have found that mild-to-moderate brain pathology is only modestly correlated with cognitive impairment [55, 56]. This individual variability in the trajectory of cognitive decline and manifestation of dementia symptoms is thought to be due to the existence of cognitive reserve—or the ability to tolerate age-related changes and disease related pathology of the brain without developing clinical symptoms or signs of disease [57]. Stern [58] suggested that cognitive reserve can take two forms: 1) neural reserve in which existing brain networks are more efficient or have greater capacity, and thus may be less susceptible to disruption; and 2) neural compensation in which alternate networks may
compensate for the pathological disruption of pre-existing networks. Mortimer [59] hypothesized that since pathological lesions can be present long before clinical symptoms of dementia occur, there are two sets of risk factors for dementia: 1) pathological risk factors; and 2) clinical expression risk factors. Irrespective of the framework by which cognitive reserve operates, there is an implicit notion within the cognitive reserve hypothesis that greater amounts of reserve will limit the clinical expression of dementia symptoms (i.e., cognitive resilience) until a threshold level of brain pathology is reached at which point cognitive reserve can no longer compensate for the underlying pathology [60].

Although the exact etiology and disease progression that occurs from healthy cognition, to MCI, to dementia is unknown, Jack and colleagues [61] proposed a hypothetical model which is worth further consideration. As described in Figure 1.1, underlying changes in older adult brain neurophysiology (due to both modifiable and non-modifiable risk factors) causes changes in brain structure and function, which leads to declines in cognitive function and clinical manifestations of dementia. Although this model was originally developed to describe the pathological cascade of AD, and thus may not be appropriate for describing the pathology of certain sub-types of dementia such as Lewy-body dementia or vascular dementia, the most common form of dementia is AD—accounting for ~50-70% of all dementia cases [62]. The model of Jack and colleagues [61] also appears to align with the concept of cognitive reserve, whereby accumulating brain pathology can be compensated for up to a certain threshold before clinical symptoms become apparent [60].

Thus, the maintenance of older adult cognitive health appears to be a complex and multi-faceted problem, whereby pathological markers of cognitive decline are necessary but not sufficient for
causing cognitive decline. It instead appears that neurophysiological markers, brain structure and function, as well as cognitive performance are each integral for maintaining older adult cognitive health and have a complex relationship with each other [61].

Figure 1.1 Hypothetical model for the biological cascade of dementia pathology (based on the model of Jack et al., 2010; [61])

Given the evidence which I have summarized above, I define older adult cognitive health as being composed of the following interrelated characteristics (Figure 1.2): 1) healthy levels of neurophysiological biomarkers which impact brain structure and function (e.g., Aβ42 deposition, Tau protein, IGF-1, BDNF, inflammatory markers, etc.; [61, 63]); 2) maintenance of brain structure including brain volume, cortical thickness, and white and gray matter integrity [38, 40]; 3) maintenance of brain function including functional activation, functional connectivity, and electrical activity [35, 51, 64]; and 4) maintenance of cognitive function for age and education levels, including global cognitive function and the cognitive sub-domains of memory and executive function [27, 65].
Figure 1.2 Characteristics and relationships of older adult cognitive health

Markers of Cognitive Health

Neurophysiological Biomarkers
(AB42 deposition, IGF-1, BDNF, inflammatory markers, etc.)

Brain Function
(Functional activation, functional connectivity, electrical activity, etc.)

Brain Structure
(Brain volume, cortical thickness, white matter and gray matter integrity, etc.)

Cognitive Function
(Global cognitive function, executive function, memory, processing speed, etc.)
1.2.2 Measuring cognitive health

It is beyond the scope of this thesis to review every measure of cognitive health. However, I will provide a general overview of the methods by which each of the four main characteristics (neurophysiological biomarkers, brain structure, brain function, and cognitive function) of cognitive health are measured.

1.2.2.1 Neurophysiological biomarkers

A “biomarker” is an objective measure which refers broadly to a number of medical signs that are used in diagnosing and assessing the progression of a disease or response to therapies [66, 67]. I define a neurophysiological biomarker as an objective measure which is related to the neurophysiological structure and function of the brain, can be found concentrated in the brain or biological fluids, and helps in diagnosing and assessing cognitive health. Broadly, neurophysiological biomarkers can be stratified into four main categories: cerebrospinal fluid (CSF) biomarkers, plasma or urine biomarkers, positron emission tomography (PET) markers, and genetic risk markers [68, 69]. While each of these biomarkers are important to the diagnosis and assessment of older adults’ cognitive health, my thesis studies have not included these markers.

1.2.2.2 Structural neuroimaging

Structural neuroimaging uses magnetic resonance imaging (MRI) as a non-invasive method for mapping static anatomical structure [70]. Structural neuroimaging is based on the magnetization properties of atomic nuclei, wherein a powerful, uniform, external magnetic field (~1.5-7T) is employed to align hydrogen protons that are normally randomly oriented within the water nuclei of brain tissue in order to develop detailed images of brain structure [71]. Typically, T1-weighted
images are used in structural neuroimaging analyses of older adult cognitive health—most often by using a semi-automated pipeline on data acquired, which is then analyzed using neuroimaging software [72-76]. These analyses can include the quantification of brain regional volume, curvature, surface area, and cortical integrity. Other structural neuroimaging techniques—such as diffusion imaging, T2-weighted imaging, and fluid attenuated inversion recovery—are outside of the scope of my thesis work, but can provide other insights into older adult neuroanatomical structure and integrity.

1.2.2.3 Functional neuroimaging

None of my thesis studies included functional neuroimaging, and thus I will only briefly describe these techniques for measuring brain function. Magnetic functional neuroimaging uses MRI to detect neuronal activation via changes in blood-oxygen-level-dependent (BOLD) signals [35, 51]. The BOLD signal can be used to create activation maps that describe the average engagement of brain regions during specific conditions in response to particular stimuli. There are two main methods of magnetic functional neuroimaging: task-based functional MRI (fMRI), and resting-state functional MRI (rs-fMRI). Electroencephalography (EEG) is a measurement tool for quantifying brain function that uses electrophysiological monitoring to record the electrical activity of the brain [77]. Magnetoencephalography (MEG) allows for real-time estimation of cortical activity by recording magnetic fields produced by electrical currents occurring naturally in the brain [78]. Single-photon emission computed tomography (SPECT) uses gamma rays that can be detected by a gamma camera in order to determine the biological function of regional brain metabolism [79], and can be used to diagnose and differentiate the different causal pathologies of dementia [80]. The technique is similar to PET, which can also be considered a functional
neuroimaging technique. Functional near-infrared spectroscopy (fNIRs) uses near-infrared light for the detection of BOLD signals in localized cerebral blood flow during specific conditions in response to particular stimuli [81].

1.2.2.4 Neuropsychological Testing

As the name implies, this method for examining cognitive health uses performance-based neuropsychological tests to measure cognitive performance. Neuropsychological testing is a hallmark of medical research to determine changes in cognitive health and potential risk factors for cognitive decline [82]. As highlighted above, some domains of cognitive function tend to change as adults age or in response to intervention [25]. These domains of cognitive function are considered to be fluid, while cognitive domains that are far less likely to change (e.g., reading ability, general knowledge, language, etc.) are defined as crystallized and by definition remain relatively constant over the normal adult’s lifespan [26]. Thus, neuropsychological tests which are used to examine changes in cognitive function that are indicative of changes in cognitive health are typically conducted on fluid abilities.

I will broadly define the domains of cognitive function which I have examined throughout my thesis. I also include a list of common cognitive measures for each domain in Appendix A; this list was synthesized during a recent systematic review that I conducted [83]. Within this review, I defined four main cognitive domains, which I will discuss throughout my thesis: 1) global cognitive function; 2) executive function; 3) memory; and 4) processing speed. I define global cognitive function as tasks which examine multiple domains of cognitive function including memory, executive function, and processing speed. Executive function is a broad set of thinking
abilities which includes planning, set-shifting, working memory, and inhibition. I define memory as a broad set of thinking abilities which include spatial memory, immediate memory, and episodic memory. Processing speed includes measures of reaction time and ability to process information quickly. Of final note, it is important that any measure of cognitive function have well-established psychometric properties including evidence of validity and reliability, sensitivity to changes over time, and a minimal clinically important difference (MCID; [84]).

1.2.3 Summary

Older adult cognitive health is a growing public health challenge since the number of older adults worldwide is increasing [13], and age is the greatest risk factor for cognitive impairment and dementia [14]. While a firm definition of the characteristics of older adult cognitive health are still needed, I define cognitive health as being composed of the following traits: 1) healthy levels of neurophysiological biomarkers which can impact brain structure and function [61, 63]; 2) maintenance of brain structure including brain volume, cortical thickness, and white and gray matter integrity [38, 40]; 3) maintenance of brain function including functional activation, functional connectivity, and electrical activity [35, 51, 64]; and 4) maintenance of global cognitive function for age and education levels, as well as in the cognitive sub-domains of memory and executive function [27, 65]. I have described each of the four methods for measuring cognitive health (neurophysiological biomarkers, structural neuroimaging, functional neuroimaging, and neuropsychological testing). Of note, my thesis measures cognitive health solely by neuropsychological testing and structural neuroimaging.
1.3 Time-use activity behaviours and their impact on older adult cognitive health: Physical activity, sedentary behaviour, and sleep

Although maintaining cognitive health in later life is a growing public health priority, there is not yet a pharmaceutical therapy to improve cognitive health or treat MCI and dementia. As a result, lifestyle and behavioural strategies are becoming an increasingly popular line of research inquiry and public interest.

While there are an infinite number of behaviours which humans can engage in throughout the day, each moment of the day is spent in one of three basic activities: sleeping, SB, or engaging in PA [3]. Each of these behaviours are mutually exclusive (e.g., one cannot engage in PA while also engaging in SB or sleep), have different energy expenditures from each other [8, 85, 86], and are physiologically distinct phenomena—both in the periphery and the brain [6, 7, 87-91]. I will thus refer to these behaviours collectively as time-use activity behaviours (Figure 1.3), since each 24-hour day is spent in some assortment of sleep, SB, and PA.

Time-use activity behaviours are also linked to the circadian clock—the ~24-hour biological clock that helps to align the sleep-wake cycle with the solar light-dark cycle [12]. Specifically, time-use activity behaviours can be dichotomized into two broad and distinct types of behaviour which comprise the circadian cycle: 1) wake-based behaviour; and 2) sleep-based behaviour. Wake-based behaviour occurs while a person is awake and out of bed and consists of both PA and SB. Sleep-based behaviour occurs only while sleeping. Together, these behaviours comprise both ends of the circadian cycle (i.e., sleep and wake). Time-use activity behaviours thus have a dynamic relationship with each other and with circadian regulation.
Figure 1.3 Time-use activity behaviours are distinct but related, and are also part of circadian regulation.

Figure 0.3

METs = Metabolic Equivalents
Within these next sections (Section 1.3.1 – 1.3.3), I will discuss how each time-use behaviour is associated with cognitive health. I will begin by discussing the effects of PA on older adults’ cognitive health (Section 1.3.1). I will next discuss the effects of SB on older adults’ cognitive health (Section 1.3.2), and then describe how sleep impacts older adults’ cognitive health (Section 1.3.3); I will review circadian physiology in my discussion of sleep, given the link between sleep and circadian physiology [12]. In each section, I will provide important definitions, review the current methods for measuring the phenomena, and then describe how each behaviour impacts cognitive health.

### 1.3.1 Physical activity and older adult cognitive health

#### 1.3.1.1 Physical activity definitions

PA is defined as a wake-based behaviour of any bodily movement produced by skeletal muscles which results in energy expenditure [92]. PA can be classified by its *duration* (i.e., time), the *frequency* that it occurs (usually in days/week), the energy expenditure required to perform it (*intensity*), the *type* of PA performed (e.g., cycling, walking, etc.), and the *context* (location as well as social setting—that is, alone versus in a group). The different types of PA can be broadly grouped into four basic domains in which PA occurs: 1) *occupational*; 2) *transportational*; 3) *household*; and 4) *leisure-time* (Figure 1.4; [93]).

PA can also be classified by the energy expenditure which is required to perform it. *Light intensity PA* (LPA) involves activities wherein energy expenditure is at a level of 1.6-2.9 metabolic equivalents (METs); or 1.6-2.9 times an individual’s energy expenditure at rest [8]. LPA includes
activities such as slow walking, cooking food, washing dishes, and standing still; it also includes activities done from a seated or lying position, which require 1.6-2.9 METs (e.g., crafts, stretching, etc.; [94]). *Moderate PA* consists of activities wherein energy expenditure is between 3.0-6.0 METs and *vigorous PA* consists of activities >6.0 METs. Evidence suggests that >150 minutes/week of PA of ≥3.0 METs has substantial benefits on numerous health outcomes [90], and thus moderate and vigorous PA are generally examined as a single construct (i.e., *moderate-to-vigorous PA* [MVPA]; ≥3.0 METs). LPA and MVPA are not exclusive to any one domain of PA, and thus all domains of PA include activities, which are LPA and MVPA.

Figure 1.4 Physical activity domains and intensities of PA

LPA: Light physical activity; MVPA: Moderate-to-vigorous physical activity; METs: Metabolic Equivalents

Current evidence suggests regular MVPA of greater than or equal to 150 minutes/week is important for older adult physical and cognitive health [90, 95]; unfortunately, greater than 95%
of older adults do not meet these recommendations [96]. Epidemiological evidence also suggests the amount of time spent engaging in each type of PA (i.e., occupational, transportational, etc.) is declining [97-100], and thus it is urgent to address the growing public health problem of physical inactivity [101].

*Exercise training* is a subcategory of leisure-time PA defined as planned, structured, and repetitive bodily movement done to improve or maintain one or more components of *physical fitness*—that is, skill- or health-related attributes which can be measured objectively [92]. Attributes of physical fitness include: 1) cardiorespiratory endurance (i.e., aerobic fitness); 2) muscular endurance; 3) muscular strength; 4) body composition; and 5) flexibility [92]. Most of the research which has examined how fitness can impact cognitive health has focused on aerobic fitness [102], since there are well defined tests to measure aerobic fitness such as the Balke Protocol and the Bruce Protocol [103].

Exercise training can also be classified according to its duration (usually in minutes), frequency (e.g., days/week), intensity (heart rate, repetition maximum, etc.), and type [104]. Maximizing the benefits of exercise training requires the precise prescription of these variables; however, the two most important variables for increasing physical fitness are intensity and *volume* (frequency x time; [105]).

The three most common forms of exercise training are *aerobic training* (AT), *resistance training* (RT), and *multimodal training* (MT; [104]). AT consists of repetitive movements specifically targeting the cardiovascular system. RT consists of muscle strengthening exercises typically
performed with free-weights or machines. MT refers to either: 1) exercise training which incorporates both AT and RT; or 2) AT and/or RT which also includes other forms of exercise training such as anaerobic, balance, agility, or flexibility training [83]. Each type of exercise training has its own distinct physiology and benefits [95, 106]. For example, AT specifically increases cardiovascular fitness (i.e., maximum oxygen uptake) whereas RT increases muscle mass and strength. Current recommendations suggest older adults regularly engage in MT, specifically: 1) moderate intensity AT five days/week for at least 30 minutes/session, or three days/week of vigorous intensity for at least 20 minutes/session; 2) moderate intensity RT at least twice per week; and 3) additional AT and RT, if possible [95]. Most forms of exercise training (including AT, RT, and MT) expend enough energy to be classified as MVPA (i.e., >3.0 METs), although some forms of exercise training can be classified as LPA (e.g., balance and flexibility training; [107]).

1.3.1.2 Physical activity measurement

PA is a complex and multi-dimensional construct, and thus the measurement of PA is challenging. I broadly define the three primary dimensions (Figure 1.5) in which PA can be measured: behavioural measurement (i.e., the type and context of PA), biomechanical measurement (the movement of the body through space), and thermodynamic measurement (how much energy is expended). Each of these dimensions of PA measurement are related; for example, one minute of walking has a different rate of force production generated by skeletal muscle and total energy expenditure, than one minute of running. However, each of these dimensions has a different unit and scale of measurement. Using the previous example, walking can be measured behaviourally as minutes, distance traveled, or context (indoors vs. outside, alone vs. in a group); the
biomechanical measurement of walking could be in torque (i.e., force production by the muscle) or total work (force x distance); energy expenditure can be measured in METs, absolute oxygen consumption (L/min), relative oxygen consumption (ml/kg/min), or kcal. Accurately measuring each dimension of PA using a single measurement tool is thus not possible, and the consensus is that there is no one best method for measuring PA.

**Figure 1.5 Dimensions of physical activity measurement**

1.3.1.2.A Subjective and objective measures of physical activity

The complex and multidimensional structure of PA has thus led to the development of a variety of methods for measuring it. These methods for assessing PA have been categorized in a variety of ways [108-111], however PA measures can be broadly classified as either subjective or objective measures (Figure 1.6). *Subjective measures* assess a person’s subjective experience or recall of PA using questionnaires, surveys, diaries, logs, or ecological momentary assessment. Subjective
Figure 1.6 Characteristics and considerations for choosing a physical activity measure

EMA: Ecological momentary assessment
measures can provide useful information on usual (or past) PA behaviour—specifically, the amounts, types and contexts in which an individual engages in PA. *Objective measures* do not require the person being measured to recall or respond, but instead use instruments (i.e., pedometers, accelerometers, heart rate monitors, multimodal sensors, calorimetry, and doubly labeled water), or systematic observation to quantify an individual’s PA.

There are benefits and disadvantages to both subjective measures and objective measures. Subjective measures are inexpensive and are easy to administer, and are thus commonly used in epidemiological and population-wide studies [112]. These methods of PA measurement also provide important information about the context in which PA occurs (i.e., where, when, and with whom); however, subjective PA measures are open to significant biases including social-desirability bias and recall bias [113]. The issue of recall bias is especially important for older adults, since older adults are more likely to experience issues with accurately recalling their past or present PA [114]. Subjective measures of PA also often fail to capture low-intensity activities (i.e., LPA; [115]). Other problems for subjective measures include issues with reliability, evidence of validity, and sensitivity to change [116]. Conversely, objective methods are considered to provide a more accurate and reliable measure of PA by eliminating recall bias; however, objective methods are more costly and require skilful administration and data interpretation [117].

Several extensive reviews can be found elsewhere on the different types of measures that exist for estimating older adult PA [118-121]. Collectively, these reviews indicate that there is no one best method for measuring PA, and each type of measure has benefits and limitations which should be carefully considered by the researcher when selecting a measure.
1.3.1.2.B Important psychometric properties of physical activity measurement: validity, reliability, population specificity, and sensitivity to change

Accurately measuring PA requires careful consideration of the psychometric properties of the tool used. Inappropriate or crude measures of PA can have serious implications on study findings, and are likely to lead to misinterpreted results and underestimated effect sizes [112]. This is especially critical in the field of older adult PA research, as I determined in a systematic review published in 2015 [122]. In this review of older adult interventions to promote PA, I determined that only 63% of the measures used to estimate PA adhered to the principles of measurement. The use of measures with unknown psychometric properties makes the conclusions drawn from such studies questionable at best, and downright wrong at worst. I will therefore briefly describe the psychometric properties that are important for the precise and accurate measurement of PA: validity, reliability, population specificity, and sensitivity to change.

The validity of the measure (i.e., the instrument) can be best described as the soundness of the interpretations of the results of a measurement by which accurate conclusions may be drawn from the results [123]. No instrument can be “validated”, but rather evidence is collected to validate the interpretations made from an instrument. There are four different types of validity: definitional, content, criterion-based, and construct [124]; when used in summation, these may add to the evidence of validity of the instrument. Criterion-based evidence is the most common evidence of validity cited for both subjective measures and objective measures of PA [122].
The reliability of an instrument refers to the degree to which measurements of the same trait are reproducible under the same conditions [125]. The reliability of an instrument is an important means by which a measure can be deemed to have accuracy and consistency [126]. As with validity, an instrument can have evidence of reliability, but this does not mean that the instrument is always “reliable”. There are two broad types of reliability evidence: norm-referenced and criterion-referenced evidence of reliability.

Population specificity refers to the characteristics of the sample in which an instrument has evidence of validity and reliability. The specificity of a population can refer to a number of different characteristics such as age, ethnicity, or sex. Researchers should avoid using tools that do not have evidence of validity and reliability for the population they are presently measuring, as this greatly reduces the ability to accurately interpret findings [108]. For example, it is unlikely that a questionnaire developed for examining children’s PA would accurately reflect the PA of older adults.

Lastly, sensitivity to change (or responsiveness) refers to the ability of an instrument to detect change over time [112]. Evidence of validity and reliability are requirements in order for the instrument to have sensitivity to change. Sensitivity to change is typically quantified using the effect sizes for paired differences. For example, an instrument with evidence of validity and reliability that aims only to categorize people as “active” or “sedentary” will likely not be a sensitive instrument for detecting subtle changes over time.
1.3.1.2.C Measuring physical activity using MotionWatch8 wrist-worn actigraphy, the SenseWear Mini Armband multimodal sensor, and the Community Healthy Activities Model Program for Seniors

I will now discuss each of the measures used in my thesis including their capabilities, limitations, and psychometric properties. The measures which I will discuss are: 1) wrist-worn accelerometry, specifically the MW8; 2) multimodal sensors (i.e., SWA); and 3) the CHAMPS questionnaire.

Wrist-Worn Accelerometry Using the MW8

Wrist-worn accelerometry (or actigraphy) is one objective field-method which is becoming increasingly popular for measuring PA [127, 128]. Accelerometry is based on basic principles of physics, namely speed and acceleration. Speed is the change in position with respect to time and acceleration is the change in speed with respect to time. Acceleration is usually measured in gravitational acceleration (i.e., 9.8 m/s²). Because acceleration is proportional to the net external forces involved in movement of a body, it is directly reflective of the energy costs of that movement [129]. Wrist-worn accelerometers, such as the MW8, therefore capture the acceleration of a body in motion which can then be translated into units of PA.

However, PA must be derived from the data outputted by a wrist-worn accelerometer. Wrist-worn accelerometers output data in an arbitrary unit of counts, which are collected and averaged over a length of time, termed an epoch. Accelerometer based studies in older adults have typically used an epoch length of 1 minute [130-132]. The data must then be translated into a rate of counts per minute (CPM). These CPM can then be categorized into a certain intensity of PA through accelerometers that have corresponding validated cut-points [96, 133]. Cut-points are used to
derive an estimation of PA amount, and the intensity at which the activity is performed [134]. Researchers can then evaluate the number of minutes a participant engages in PA for a given intensity, over the duration of a specific observation period (e.g., 7 days; [135]). Calibrating a wrist-worn accelerometer to provide estimates of PA from indirect calorimetry can thus provide criterion evidence of validity.

Hence, I calibrated the MW8 to provide estimates of PA for older adults [136]. Briefly, I concurrently measured indirect calorimetry and MW8 uniaxial actigraphy worn on the non-dominant wrist during 10 different activities of daily living in 23 community-dwelling older adults (aged 57-80 years). I then determined cut-points for LPA and MVPA using receiver operating characteristic (ROC) curves. In this study, I also determined the MW8 had good evidence of inter-rater reliability (r= 0.981). In a subsequent paper, I determined the MW8 had good evidence of interclass reliability for measuring PA following ≥5 days of observation [137]. I highlight the psychometric properties of the MW8 for measuring PA in Appendix B.

**SWA Multimodal Sensor**

The SWA is a multimodal sensor which also has good evidence of validity and reliability for measuring PA across multiple populations [85, 138-143]. Briefly, the SWA integrates information from a biaxial accelerometer and other physiological sensors (heat flux, temperature, and galvanic skin cell response sensors) to provide estimates of energy expenditure in METs which can then be translated into estimates of PA. The use of multimodal sensors provides increased sensitivity for detecting subtle changes in energy expenditure associated with complex lifestyle tasks and with subtle changes in energy expenditure associated with carrying loads, walking up grades, or doing
non-ambulatory activities [144]. The SWA thus provides highly precise estimates of PA for older adults, which can be used to measure changes in PA over time [145].

**CHAMPS PA Questionnaire**

The CHAMPS questionnaire is a subjective measure with evidence of validity and reliability for measuring older adult PA [146-149]. The questionnaire is also sensitive to changes in PA [150, 151]. The questionnaire consists of 40 separate questions, which asks participants to recall different activities performed in a typical week over the past four weeks.

**1.3.1.2.D Summary**

Measuring PA is a complex and challenging issue for researchers to consider when designing a study and interpreting results. I have broadly described the different means by which PA can be measured, the psychometric properties which are important for determining the appropriateness of a PA measure, and have provided an overview of the strengths and limitations of the different measures of PA which I have used in my thesis work. I will now summarize the current body of evidence for how PA can impact older adult cognitive health.

**1.3.1.3 Current evidence examining the impact of physical activity on older adult cognitive health**

There is a plethora of evidence which indicates that PA can promote older adult cognitive health [102, 152-154]. Broadly, the literature falls into one of three separate categories: 1) observational studies examining the associations of lifestyle PA with cognitive health (Section 1.3.1.3.A); 2) randomized controlled trials (RCTs) examining the effects of exercise training on cognitive health
(Section 1.3.1.3.B); and 3) animal models to determine the mechanism by which PA and exercise training impact cognitive health (Section 1.3.1.3.C). I will therefore discuss each of these areas of literature separately.

1.3.1.3.A  **Impact of lifestyle physical activity on older adult cognitive health**

In this section I will discuss the current evidence for how lifestyle PA—that is, PA performed across all domains and intensities, both planned and unplanned—can impact older adult cognitive health. Most of the evidence for how lifestyle PA can impact older adult cognitive health comes from epidemiological studies, and is thus associative rather than causal. However, as I will highlight throughout these next three sections (Sections 1.3.1.3.A, B, and C), the current evidence meets each of the nine Bradford Hill Criteria for determining causal inference from observation studies [155]:

1) an effect size of small-to-moderate size;
2) consistent and reproducible relationships;
3) evidence of temporality in the association;
4) specificity of the relationship when controlling for confounding variables;
5) preliminary evidence of a dose-response relationship;
6) a plausible mechanism for how PA impacts cognitive health (explained in more detail in Section 1.3.1.3.C);
7) coherence between epidemiological and laboratory findings (Section 1.3.1.3.C);
8) experimental evidence from exercise training studies that PA in the form of exercise training improves cognitive health (Section 1.3.1.3.B and C); and
9) analogous associations between PA and other aspects of health.
The collective evidence from observational studies indicates that PA is associated with better cognitive performance and decreased incidence of dementia among older adults independent of other behaviours and preexisting factors [5]. In a meta-analysis of 16 prospective studies that examined the incidence of neurodegenerative disease based on PA at baseline, Hamer and Chida [156] determined that more PA was associated with a 28% lower risk of developing all-cause dementia and a 45% lower risk of developing AD, after adjusting for confounding variables. A second meta-analysis of 15 prospective studies among individuals without dementia determined that higher PA was associated with a 38% lower risk of cognitive decline, while low-to-moderate PA level was associated with a 35% lower risk [157]. Importantly, a more recent study which was not included in these meta-analyses determined that moderate-to-high PA level may be especially protective against future cognitive decline among older adults with healthy cognition at baseline [158].

Epidemiological studies have also examined how PA is associated with brain structure and function. For example, Erickson and colleagues [159] examined how regular PA can impact brain structure in a sample of 299 community-dwelling older adults with normal cognitive function at baseline. At baseline, participant PA was quantified as the number of blocks walked in the past week; structural MRIs were acquired 9 years later, and clinical adjudication for cognitive impairment was performed 4 years after the MRIs (i.e., 13 years since baseline). The authors determined that greater PA at baseline was associated with greater gray matter volumes in the frontal, occipital, entorhinal, and hippocampal regions. Greater gray matter volume was also associated with a two-fold reduction in the risk of cognitive impairment. Gow and colleagues [160]
found that over a three year period (from age 70-73) greater amounts of self-reported PA were associated with: 1) less atrophy in total brain volume; 2) greater gray matter volume; and 3) greater integrity of white matter.

Other recent work has examined the effects of maintaining PA level over an extended period of time. Best and others [161] examined how PA maintenance over a 13-year period was associated with changes in older adults’ cognitive function and brain structure. One-hundred and forty-one older adults aged 70-79 years at baseline (60% female) were annually queried about their self-reported time spent walking from years 1 to 10. Structural MRIs were performed at years 10 and 13. The authors determined that independent of initial time spent walking, demographics, and APOE-ε4 status (a genetic risk factor for AD [162]), better maintenance of time spent walking over the decade predicted less atrophy in hippocampal volume, better maintenance of gray and white matter integrity, and preserved cognitive function. Interestingly, PA at baseline and at year 10, as well as changes in PA over a five-year period, were less predictive of future changes in brain structure and cognition. These data thus appear to suggest that how PA levels change over longer periods of time may be an important contributor to cognitive and neural protection.

The positive association between PA and cognition in older age appears to be related to sparing of gray matter volume of brain regions susceptible to age-related atrophy, including the frontal and prefrontal lobes and the hippocampus [163]. Midlife PA level is also associated with larger total brain volume and gray matter volume of the frontal cortex 21 years later [164]. Dougherty and colleagues [165] determined that people who are more at risk for AD (defined in this study as either parental family history or carrying the APOE-ε4 allele), but have PA levels which meet or
exceed the current guidelines, have significantly larger temporal lobe volumes compared with individuals who did not meet the current PA guidelines.

The findings which I have described above all used subjective measures of PA; however, results from studies using objective measures also indicate PA is associated with better cognitive health. For example, Buchman and colleagues [166] reported that greater total daily PA – assessed by 10 days of hip-worn accelerometry – was associated with a two-fold reduced risk of AD over a four-year period in 716 older adults. Yuki and colleagues [167] investigated whether objectively-measured PA at baseline was associated with reduced brain atrophy (mean follow-up duration of 8.2 years) among 774 Japanese older adults. Participants in the highest quintile of PA had a significantly lower risk of frontal lobe atrophy compared with participants in the lowest quintile of PA.

There is also preliminary evidence suggesting that higher amounts of LPA, such as household chores may also help maintain brain health and cognitive function [168, 169]. Most of the literature has examined the relationships of total PA (i.e., LPA + MVPA) or MVPA with cognitive health [5, 170], and thus more research is needed as to whether LPA can also promote cognitive health.

While the collective evidence to date therefore suggests that PA can help reduce dementia risk, these findings cannot determine the optimal dose of PA to maintain cognitive health. Thus, while the dose-response relationship between PA and other health parameters is well established (i.e., the greatest benefits in health are seen in becoming physically active, with smaller health benefits for greater amounts of activity), the dose-response relationship between PA and cognitive health...
is still relatively unclear [95]. However, Xu and colleagues [171] recently conducted a preliminary meta-analysis of five studies wherein they investigated the dose-response relationship between self-reported PA and cognitive health. The authors determined that for every 500 kcal/week of energy expenditure from PA, there was a 10% and 13% decrease in the risk of all-cause dementia and AD, respectively. Evidence is still needed on the dose-response relationship between PA and cognitive health using objective measures of PA.

Another key limitation of prospective cohort studies is that causality cannot be established and the potential for unmeasured confounding variables are often present. Of particular importance, the positive associations observed in prospective cohort studies may be due to reverse causality; meaning that people who engage in more PA have a more robust genetic profile against cognitive impairment and dementia [153]. Conversely, those with very prodromal manifestations of cognitive decline may be less inclined to engage in PA. Sabia and colleagues [172] examined participants from the Whitehall II Cohort Study, finding that there was no association between PA and subsequent cognitive decline 15 years later. The authors also determined that there was no association between PA and risk of dementia over an average 27 year follow-up. Critically, PA in people with dementia began to decline up to 7 years before diagnosis, which seems to indicate that lower risk of dementia in physically active people may be attributable to a decline in PA levels in the preclinical phase of dementia.

A final and important limitation of the current literature is that most of the causal evidence for PA improving cognitive health comes from studies of exercise training [5, 173], as described in
Section 1.3.1.3.B. Thus, it is currently unclear whether increasing lifestyle PA (either LPA or MVPA) is sufficient to improve cognitive health.

1.3.1.3.B Impact of exercise training on older adult cognitive health

In this section, I discuss exercise broadly without reference to type of the exercise (i.e., AT, RT, or another form of exercise training). The early literature on the importance of exercise for older adult cognitive health examined the importance of physical fitness—specifically aerobic fitness—for cognitive function [102, 174]. These literature reviews found conflicting results. One of the reviews found increased physical fitness was associated with improved cognitive performance [102], while the later study did not find improved aerobic fitness was associated with greater cognitive performance [174]. It is important to note that the first review only included RCTs, while the second investigated cross-sectional and non-randomized designs, which suggests that lower quality studies may have confounded the results of the later review.

In addition to examining the effects of fitness on cognitive health, early reviews have used heterogeneous age groups and populations—from both animal and human data. Collectively, these data also suggest improved fitness can enhance older cognitive health and even prevent cognitive decline [175, 176]. Converging evidence at the cellular, molecular, behavioral, and systematic levels also suggest exercise has beneficial effects on cognitive health across all age groups [177-180]. However, most of these data are based on the findings of trials which have used AT as the exercise intervention, and there is still limited knowledge about how RT and other types of exercise training can impact cognitive health [106, 181, 182]. As such, developing and designing exercise
programs to promote cognitive health are not fully addressed within these review papers, and there remains an issue in translating interventions from the laboratory to the outside world [175-180].

More recent reviews have begun to examine how exercise training can promote cognitive health in people with cognitive impairment. Heyn and colleagues [183] initially determined in a meta-analysis of 30 studies among people with dementia and related cognitive impairments that exercise training significantly improved cognitive function; although the authors did not determine which domains of cognitive function were most impacted by exercise training. In a subsequent meta-analysis of 14 RCTs among older adults with MCI, Gates and colleagues [184] determined that exercise training had a small but significant effect on verbal fluency, but did not improve response inhibition, cognitive flexibility, memory, or processing speed. Most recently, Zheng and colleagues [185] conducted a meta-analysis of 11 RCTs which examined whether AT improved cognitive function among older adults with MCI. The authors determined that AT had a large effect on global cognitive function, modestly improved immediate and delayed memory, and significantly improved executive function. While these data suggest MCI is a window of opportunity to promote cognitive health through exercise training, less is known about how other training modalities beyond AT (i.e., RT, MT, etc.) can promote cognitive health.

Several meta-analyses published in the last two years also warrant consideration. In a comprehensive systematic review and meta-analysis, Northey and colleagues [154] determined that exercise training has a modest effect (Cohen’s $d= 0.29$) on the cognitive function of older adults over the age of 50 years—both for individuals with and without cognitive impairment. The authors also determined that AT, RT, MT, and Tai chi exercise could each improve the cognitive
function of older adults, although it was unclear which type of exercise training was most beneficial; yoga did not significantly improve cognitive function. Moderate and vigorous intensity exercise were also significantly beneficial to cognitive function, while low intensity exercise was not. Exercise training also benefitted the cognitive domains of attention, executive function, and memory; however, the effect sizes for each domain were overlapping. The authors thus recommended that older adults should perform exercise training in the form of MT to improve cognitive function, and that improvements were independent of baseline cognitive ability. The authors also found that the effect of exercise on cognitive function was slightly larger for individuals without MCI ($d = 0.36$) compared with older adults with MCI ($d = 0.28$). However, the confidence intervals for these estimates were overlapping, and there was a significant effect of exercise on cognitive function for individuals with and without MCI.

More recently, in a systematic review of 98 studies in older adults ≥60 years of age, Gomes-Osman and colleagues [186] suggested that >52 hours of exercise training was associated with improved cognitive performance in older adults with and without cognitive impairment. However, this finding was not based on any meta-analysis, but on the median length of intervention volume (in hours) for studies which reported improvements in cognitive function. These results, thus need to be treated with extreme caution, and it is unlikely that 52 hours of exercise training represents some sort of magic number to elicit improvements in cognitive function.

There has also been increasing interest in whether there are sex-differences in the effects of exercise training on older adult cognitive function. In a systematic review and meta-analysis of 39 studies, Barha and colleagues [187] determined that exercise training interventions with a high
proportion of females (defined as >71% female) had significantly greater effects on executive function compared to studies with a lower proportion of females (≤71% female). A separate systematic review and meta-analysis of 17 animal studies by Barha and colleagues [188] also found sex differences in the effects of exercise training on cognition between male rodent studies and female rodent studies.

Of final note, I recently published a systematic review and meta-analysis to examine the effects of exercise training on the physical and cognitive function of older adults (60+ years; [83]). This review of 48 studies provides five important updates to the literature. First, my review provides an important update to the recommendations made in Northey and colleagues [154] by now suggesting that MT is beneficial to both cognitive function and physical function. Second, my review distinguished between primary and secondary outcomes of cognitive function; the results indicated that the effects of exercise training on cognitive function are smaller than what has been previously reported (Hedge’s $g= 0.24$). Third, I determined that the precise estimate of the effects of exercise training on cognitive performance appears to be hampered by use of heterogeneous samples which include people of different physical (i.e., frail vs. healthy) and cognitive statuses (MCI vs. healthy), such that studies which include samples of mixed cognitive and physical statuses may be diluting the effects of exercise training by potential deviations from the exercise protocol. Fourth, unlike past meta-analyses which examined sex differences in exercise efficacy as a categorical variable [102, 187, 188], I examined sex as a continuous moderator (i.e., %female) and did not find that it moderated the effects of exercise training on cognitive function. While this study suggests that the sex-specific effects of exercise on cognitive function are less robust than originally suggested, meta-analyses examining the disaggregated sex-specific effects of exercise
are still needed. Lastly, I determined that exercise-induced improvements in physical function are associated with improvements in cognitive function at the study level, which provides support for the central benefit model—whereby cognitive and neural plasticity may be an important mechanism by which exercise training promotes mobility [189].

The evidence therefore suggests that exercise training can help reduce dementia risk. However, it is still unclear what the optimal dose of exercise is to promote cognitive health [106]. For example, little is also known about whether engaging in AT, RT, MT, or some other type of exercise training (e.g., anaerobic training, power training, etc.) will yield optimal cognitive benefits. In addition, there is preliminary evidence that genotypic differences may moderate the effects of exercise training [190], however this area of research is still under investigation and is far from conclusive. Future research is needed to 1) examine ways to ensure exercise training programs provide maximal benefits to older adult cognitive health; 2) determine the dose-response relationship between exercise and cognitive health; and 3) whether biological sex and genotypic differences moderate the effects of exercise on cognitive health.

Current interventions are now focused on assessing the effects of different types and intensities of exercise training for promoting cognitive health among people with MCI. Baker and colleagues [191] examined the efficacy of high-intensity AT on cognitive function in older adults with MCI. Participants (N= 33) were randomized to either 6 months of 4 days/week high intensity AT or a stretching control group. The high-intensity AT group trained at 75-85% of heart rate reserve for 45 to 60 minutes per session. The stretching control group carried out supervised stretching activities according to the same schedule but maintained their heart rate at or below 50% of their
heart rate reserve. Interestingly, the high-intensity AT group improved cognitive function in women, but not men. While these results appear to suggest a sex-specific effect of exercise, the sample size was small—especially with regard to the sex-stratified analyses.

More recent evidence suggests AT may augment cognitive function in those with MCI by improving neural efficiency [192, 193]. Among 70 older adults with mild vascular cognitive impairment, Liu-Ambrose and colleagues [193] showed that six months of AT significantly improves global cognitive performance compared with a usual care plus education group. Examination of secondary measures showed between-group differences at intervention completion favouring the AT group in 6-minute walk distance and in diastolic blood pressure. A subset of participants participated in a functional MRI study [192], which determined that compared to the control group, AT significantly reduced activation in the left lateral occipital cortex and right superior temporal gyrus. Reduced activity in these brain regions was significantly associated with improved executive function performance on the flanker task at trial completion. The results of the partial correlation analysis support the notion of neural efficiency, which is defined as the level of activity a neural network requires in order to complete the task at hand [194].

Erickson and colleagues [195, 196] determined that AT can positively impact hippocampal volume and memory among healthy older adults. Subsequently, ten Brinke and colleagues [197] extended this work by demonstrating that compared with balance and tone exercises, thrice-weekly AT significantly increases left, right, and total hippocampal volumes in older adults with MCI.
Recent RCTs have also begun to investigate the impact of RT on older adult cognitive function, especially among individuals at risk for dementia. In 86 older women with MCI, Nagamatsu and colleagues [198] demonstrated that compared to a balance and tone control group, 6 months of twice-weekly moderate intensity RT significantly improved executive functions—specifically, the cognitive processes of selective attention and conflict resolution. The authors also found improvements in associative memory – or the ability to remember items presented simultaneously. In conjunction, regional patterns of functional plasticity were found in the RT group, whereby three key regions in the cortex showed greater functional activation during an associative memory task after 6 months training—the right lingual gyrus, the right occipital-fusiform gyrus, and the right frontal pole. Interestingly, improvements observed in executive performance occurred after only 6 months of RT in those with MCI, compared to 12 months in otherwise cognitively healthy older adults [199]. It is thus possible that the benefits of RT may be observed earlier in those with cognitive deficits [5], although more evidence is needed to confirm this hypothesis.

The SMART (Study of Mental and Resistance Training) trial [200] also demonstrated the positive impact of RT on cognitive health in older adults with MCI. One-hundred older adults with MCI were randomized to two interventions: 1) a high intensity RT group or a seated calisthenics group; and 2) a computerized cognitive training group or a sham cognitive training group. Participants completed both interventions 2-3 days/week for 6 months with an 18-month follow-up. The investigators found that RT but not computerized cognitive training significantly improved global cognitive function as well as expanded gray matter in the posterior cingulate. Interestingly, these improvements were related to each other (r= 0.25). RT also significantly reduced the progression of white matter lesions.
More studies are now examining the effects of exercise training among older adults with dementia. In a 12-month RCT of 210 older adults with AD [201], researchers randomized participants to either home-based exercise, group-based exercise, or usual care for 12 months. Participants in either of the exercise programs were encouraged to engage in two 1-hour sessions of MT per week. Although the data did not support a significant effect in the most rigorous analyses, the authors suggested that home-based exercise improved executive function compared to the usual care group. The group-based exercise program produced intermediate effects and did not differ compared to either the usual care or home-based exercise participants.

Lamb and colleagues [202] recently conducted a large RCT of 494 people with dementia which examined the effects of 4 months of supervised moderate- to high-intensity MT plus unsupervised home-based exercise training on ADAS-Cog performance at 6 and 12 months. Compared with the usual care control group, the exercise group showed slight declines in ADAS-Cog performance at 12-months. However, it is important to note that rather than examining the effects of the intervention immediately following trial completion (i.e., 4 months), cognitive performance was not measured until 6 and 12 months (i.e., 2 and 8 months after the end of the trial). The delay in assessing treatment outcomes makes it very difficult to determine the true effect of the intervention as it seems unlikely that individuals with dementia would continue with the exercise program during the post-trial period.

Together with the previous studies on MCI, it is plausible that a modest degree of cognitive decline might be ameliorated by exercise training, yet more severe cognitive decline might be less
ammmenable through exercise training. Even so, it is noteworthy that in the 2018 practice guideline summary for MCI, the American Academy of Neurology states that while no high-quality evidence exists for pharmacological treatment of MCI, exercise is likely to provide benefit [203].

Of final note, there has been some recent interest in the effects of other types of exercise training – specifically anaerobic training - on older adult cognitive health. Briefly, anaerobic training (or high intensity interval training [HIIT] as it is commonly known) uses higher intensity cardiovascular exercise which is at or above a person’s anaerobic threshold—the point at which the body can no longer meet immediate energy production needs using only beta oxidation and aerobic respiration, and begins to also produce energy through glycolysis [104]. Because of the high intensity of the exercise, it cannot be sustained continuously for long periods of time and is often performed in shorter intervals (hence the name HIIT). There is a growing interest in HIIT since 1) it might be a quicker and more time-effective means of delivering exercise as a therapy; and 2) observational data appears to suggest that higher intensity PA provides greater benefits to cognitive health than lower intensities [204, 205]. To this end, Kovacevic and colleagues [206] recently conducted a quasi-experimental study of 64 healthy older adults which examined the effects of thrice-weekly HIIT as compared with AT or a stretching control group. The results indicated that the HIIT group had significantly better memory performance than the AT and control group. While this preliminary work is interesting, these results must be treated with extreme caution since participants were not randomized at baseline. Future work using rigorous empirical methods is needed to determine the efficacy of HIIT as an intervention strategy for promoting older adult cognitive health.
Summary

The precise characterization of optimally effective exercise training has yet to be fully elucidated. For example, it is unclear whether AT, RT, or MT is most beneficial for cognitive health. Maximizing the benefits of exercise training for cognitive health will require the precise prescription of volume (i.e., frequency*duration) and intensity that are based on the best-available evidence. It is also unclear if the effects of different modalities of exercise training are domain-specific or global. Although there has been some recent debate as to what aspects of cognitive function are impacted (or not) by exercise training [207-209], the overwhelming evidence to date suggests that exercise training can impact global cognition, processing speed, executive functions, and memory [106]. Future research is needed to determine: 1) the most beneficial intensity, frequency, and duration of exercise necessary to improve cognitive health; 2) whether AT, RT, or a combination of AT and RT is more beneficial for cognitive health; 3) how other types of exercise training (such as anaerobic and power training) can impact cognitive health; and 4) whether promoting exercise training should be done in the early, later, or mid-stages of cognitive decline.

1.3.1.3.C Mechanisms by which physical activity and exercise training can impact older adult cognitive health

To date, most of the literature examining the mechanism by which PA impacts cognitive health comes from animal models of AT [179, 180]. Because exercise is a sub-category of PA, it is believed that the mechanisms by which PA and exercise improve cognitive health are similar. Broadly, the current evidence suggests that PA stimulates neurogenesis and angiogenesis, with the greatest effects being found in the dentate gyrus of the hippocampus [180]; these improvements are associated with improved memory and learning capability [177]. Animal models have also
found that older animals also see significant increases in neurogenesis and angiogenesis, as well as improved ability on a memory task [178]. However, these findings are broadly based on models of exercise training, wherein an animal undergoes a set volume, intensity, and type of exercise training.

As discussed previously, the two most common forms of exercise training are AT and RT, or sometimes used in combination as MT. Each type of exercise training has its own distinct physiology and benefits [104]. For example, AT specifically increases cardiovascular fitness (i.e., maximum oxygen uptake) whereas RT increases muscle mass and strength. Importantly, each type of exercise training has beneficial effects on cognitive health [106]. Given AT and RT are distinct behaviours with their own physiology, I will review the current evidence for the mechanisms by which AT and RT impact cognitive function separately. The mechanism by which MT impacts cognitive health is unknown. I will begin each of these sections by discussing the evidence for the mechanisms from animal models and then discuss the evidence from human models.

**Mechanisms by which AT Impacts Cognitive Health**

Much of the literature examining the molecular and cellular effects of AT comes from animal models. In these studies, the exercise is manipulated by providing voluntary access to a running wheel or by forced exercise on a treadmill. Animal models have focused on three mechanisms by which AT may influence cognitive health: 1) neurogenesis or the creation of new neurons [179]; 2) cerebral angiogenesis or the creation of new blood vessels in the brain [210]; and 3) changes in inflammatory markers [180].
Neurogenesis

The most studied mechanism by which AT can influence cognitive health is exercise induced neurogenesis in the hippocampus, specifically the dentate gyrus [179, 180, 211-214]. As illustrated in Figure 1.7, AT stimulates neurotrophic factors in the periphery and in neuronal cells of the brain [179, 180].

There are several important neurotrophic responses which occur with AT. Perhaps most importantly, AT causes an increase in firing of pyramidal cells of the hippocampus [215], which is thought to stimulate brain derived neurotrophic factor (BDNF) production [6]. In addition to up-regulation of BDNF, vascular endothelial-derived growth factor (VEGF) increases in the periphery in response to AT and crosses the blood-brain barrier to enter the brain [216]. Insulin-like growth factor-1 (IGF-1) is also up-regulated and can also cross the blood-brain barrier to enter the brain; however, it is also centrally derived [217]. There is also some evidence suggesting the importance of serotonin for exercise neurogenesis, although little is known about the mechanism [218]. Thus, it appears that up-regulation of BDNF, VEGF, and IGF-1 are all neurotrophic responses to AT.

Both BDNF and IGF-1 are closely involved in neurogenesis in response to AT, however the relationship between IGF-1 and BDNF to modulate aspects of exercise-induced neurogenesis is complex [219]. Briefly, exercise induced expression of BDNF and IGF-1 are regulated in the hippocampus through their cognate receptors (tyrosine kinase B [TRKB] and insulin-like growth factor I-receptor [IGF-1R], respectively; [219, 220]). Both TRKB and IGF-1R induce activation of the calmodulin kinase II (CAMKII) and mitogen-activated protein kinase (MAPKII) pathways; these pathways interface to up-regulate centrally derived IGF-1 and BDNF [221]. In addition,
Figure 1.7 Hypothesized mechanism through which IGF-1 signaling may interface with BDNF-mediated synaptic plasticity in the hippocampus during exercise

BDNF = Brain Derived Neurotrophic Factor; CREB = Phosphorylated Cyclic AMP Response Element Binding Protein; IGF-1 = Insulin-like Growth Factor 1; IGF-1R = Insulin-like Growth Factor 1 Receptor; LTP = Long Term Potentiation; p-CAMKII = Phosphorylated Calmodulin Protein Kinase II; p-MAPKII = Phosphorylated Mitogen-activated Protein Kinase II; pro-BDNF = precursor BDNF; TRKB-R = Tyrosine Kinases B Receptor; VEGF = Vascular Endothelial-derived Growth Factor. Modified from Cotman, Berchtold, & Christie 2007 [180].
expression of CAMKII and MAPKII up-regulates Synapsin I and Synaptophysin [220]. Synapsin I tethers synaptic vesicles to each other and to the actin cytoskeletal net, thus functioning to maintain proper synaptic transmission of neurotransmitters [222]. Synaptophysin is a key protein in the biogenesis of synaptic vesicles from cholesterol and may possibly facilitate membrane retrieval during vesicle recycling [223]. Expression of these proteins may thus be an important component of maintaining cytoarchitecture during and after neurogenesis. Finally, both CAMKII and MAPKII up-regulate expression of cyclic-AMP response element binding protein (CREB; [224]). CREB is critical for activity-dependent long-term neuronal plasticity and is believed to be necessary for the formation of long-term memory [6].

There are also still gaps in the understanding of the mechanisms by which BDNF, IGF-1 and VEGF stimulate neurogenesis. For example, it is unknown whether VEGF has an independent mechanism by which it stimulates neurogenesis [180], although VEGF does appear to be necessary for neurogenesis to occur [216]. It is also unclear by what mechanism BDNF stimulates neurogenesis in the hippocampus [211], although AT increases BDNF signaling and concomitantly increases cell proliferation and neurogenesis [225, 226]. Evidence also suggests IGF-1 mediates neurogenesis in the hippocampus [217], although the precise mechanism of this process is still under investigation. What is clear, however, is AT increases cellular proliferation, dendritic complexity, and dendritic spine density in the dentate gyrus of the hippocampus [227-230]. These adaptations in the hippocampus are associated with improvements in learning and memory [179, 180, 214]. Importantly, adaptations in cytoarchitecture also occur in older and diseased animals [231-235], suggesting the importance of AT for neurocognitive health across populations.
**Angiogenesis**

The concomitant effect of AT on cerebral angiogenesis may be necessary to stimulate increased neurogenesis [236]. While the effects of BDNF on angiogenesis are largely unknown, both IGF-1 and VEGF are necessary to induce cerebral angiogenesis [237, 238]. Increased signaling of IGF-1 and VEGF are associated with endothelial cell proliferation, and increased vessel size and branching, and thus parallel generation of new neural cells in the dentate gyrus of the hippocampus [236]. As such, angiogenesis may be a necessary component of neurogenesis—increasing blood-flow to newly synthesized neural tissue in order for it to be utilized and properly maintained. Angiogenesis may thus support improvements in memory and learning through its involvement in neurogenesis [179, 180]. Importantly, this finding has been replicated in older and diseased animals [231].

**Down-regulation of Inflammatory Markers**

AT is also linked with other improvements in neurophysiology—specifically by down-regulating inflammatory factors, which are associated with the progression of AD. For example, AT significantly reduces Aβ protein levels in the frontal cortex of transgenic mice predisposed to AD symptoms [239]. In addition to reducing Aβ load, AT in transgenic mice reduces pro-inflammatory markers including IL-1β and TNF-α [240]. Importantly, both of these inflammatory markers are associated with increased Aβ load and have been linked to AD progression [241, 242]. Immune-response proteins also significantly increase in response to AT [241, 242], and thus may help delay disease progression.
Evidence from Human Trials

There has also been a growing amount of interest in applying the knowledge gained from animal models, to understanding the mechanisms by which exercise training can promote cognitive health in humans. AT is consistently linked with increases in neurotrophic factors [243]; however, human studies cannot directly assess central BDNF, IGF-1, or VEGF, and it is not feasible to assess the time course by which neurotrophic factors impact cognitive health.

While few studies have reported on how these growth factors impact cognition, two studies have investigated how these growth factors can impact brain plasticity and function [196, 244]. Neither study found circulating levels of BDNF, IGF-1 and VEGF changed after one year of AT. However, change in BDNF was associated with increased hippocampal volume in one study [196]; in the other study, increased serum BDNF, IGF-1, and VEGF were associated with increased functional connectivity of the bilateral parahippocampus and the bilateral middle temporal gyrus [244]. While neither study reported whether increases in growth factors were associated with improvements in cognitive function, the results appear to align with findings from animal studies which suggest these neurotrophins contribute to the positive effects of exercise on cognitive health [179].

While the precise mechanism by which AT stimulates a neurotrophic response is yet unclear, there is evidence that higher cardiorespiratory fitness is linked with greater brain volume [175, 176, 245], and there is growing evidence that AT (which also improves cardiorespiratory fitness [104]) is associated with increases in brain volume in aging humans [246, 247]. The areas which seem to be most affected by AT are the prefrontal and medial temporal areas of the brain [196, 197].
Human trials cannot directly assess changes in neurotrophins as a result of AT; although it appears serum changes in BDNF are associated with changes in brain health [196].

**Mechanisms by which RT Impacts Cognitive Health**

Much less is known about the neurophysiological impacts of RT on cognitive health. This dearth of knowledge is due to the only recent development of animal models to examine the effects of RT [248]. Within this model, the mouse or rat is familiarized with a vertical ladder apparatus which has a shelter located at the top of the ladder. Once the animals learn to climb the apparatus, they are progressively loaded with a weight to their tail in order to mimic a progressive RT program.

The mechanism by which RT impacts cognitive function is much different than the mechanism of AT [249]. The largest difference in the mechanisms of AT and RT is the signalling of IGF-1 and BDNF [219, 250]. Paradoxically, while IGF-1 signalling is required in order to stimulate AT induced neurogenesis [219], AT seems to have little or no influence on peripheral IGF-1 levels [250]. By comparison, peripheral IGF-1 increases with RT while peripheral BDNF levels do not appear to be altered. To my knowledge, no study has examined what the effects of RT are on VEGF in animal models; however, one human study found thrice weekly RT increased peripheral VEGF [251]. Another human study using a combination of RT and AT found peripheral VEGF levels increased following the intervention [252]. Neither of these human studies examined whether VEGF changes were associated with improvements in cognitive performance.

Other important differences in the mechanism of RT, as compared with AT, are worth mentioning. One study compared an eight week RT protocol to eight weeks of AT [249]. Briefly, the results of
this study indicate RT and AT can both improve cognitive function, but do so through divergent mechanisms. Interestingly, hippocampal IGF-1 increased for both the RT group and the AT group; although the RT group did not appear to increase expression of BDNF. Both groups also had increased expression of Synapsin I and Synaptophysin; however, the RT group had significantly greater Synapsin I expression than the AT group. Preliminary evidence also suggests RT may stimulate neurogenesis and reduce apoptotic cell signalling in the hippocampus [253], although a recent study did not find an effect of eight weeks of RT on neurogenesis [254]. Thus, the mechanisms by which RT may impact neurophysiological health are still unclear.

Evidence from Human Trials

The precise mechanisms by which RT affects cognitive health remain under investigation; however, the evidence does indicate RT can have beneficial effects on both brain plasticity and cognitive function in older adults. Specifically, RT for older adults can improve executive function and memory [198, 199, 255]. Twice weekly RT for 12 months may also have a long term effect on executive function, memory, and cortical white matter volume [256]. In addition, RT in older adults may increase cortical thickness in the posterior cingulate gyrus, decrease functional connectivity between the posterior cingulate and anterior cingulate cortex, and increase functional connectivity between the hippocampus and the left superior frontal lobe cluster [257]. These data suggest RT may help alter and improve functional connectivity in older adults, specifically the default modal network and the frontal-temporal network.

1.3.1.4 Summary of the current evidence examining how physical activity impacts older adult cognitive health
There is a large body of evidence which indicates that PA is important for healthy cognitive aging. Most of the evidence linking PA to healthy cognitive aging comes from observational data; however, exercise training RCTs and animal research both indicate that PA in the form of exercise can improve multiple aspects of cognitive health. While it is thus clear that PA is a pillar of healthy cognitive aging, researchers need to carefully consider how to measure PA in order to best understand its impacts on cognitive health. The precise dose-response relationship between PA and cognitive health also remains unclear, and it is unclear whether different types of PA will have different effects on cognitive function. A considerable amount of research has also examined how exercise training (a sub-domain of PA) can promote older adult cognitive health, specifically in the domains of memory and executive function. The mechanism by which PA promotes cognitive health is also based on animal models of exercise training; however, it is still unclear whether AT, RT, or MT is most beneficial for older adult cognitive health. Future research is still needed to address a number of areas including: 1) what types and intensities of PA and exercise training are most beneficial for older adult cognitive health; 2) which cognitive functions and areas of the brain are specifically targeted by each type of PA and/or exercise training; 3) the underlying mechanisms by which PA and exercise training impacts older adult cognitive health; and 4) the dose-response relationship between PA and cognitive health.

1.3.2 Sedentary behaviour and older adult cognitive health

1.3.2.1 Definition of sedentary behaviour

SB is defined as any wake-based behaviour which incurs ≤1.5 METs and includes behaviours such as sitting, television watching, and lying down [8]. A common misconception is SB is the inverse
of PA; however, SB is an independent behaviour with its own distinctive effects on health [258].

Like PA, SB can also be classified by it’s duration, frequency, type, and context; SB is not classified by it’s intensity since all SB requires low energy expenditure. Tremblay and colleagues proposed that SB should be classified according to the SITT formula [88], consisting of:

1. SB frequency (number of bouts of a certain duration);
2. Interruptions (e.g., getting up from the couch while watching [259]);
3. Time (duration of sitting); and
4. Type (mode of sedentary behaviour such as TV viewing, driving a car, or computer use; Figure 1.8)

The context of where SB occurs (and who with) can also have important implications on health [260].

**Figure 1.8 Different types of sedentary behaviour**

1.3.2.2 Sedentary behaviour measurement

There are a few differences between measures of SB and measures of PA that are worth mentioning. Given that SB is a distinct and independent behaviour from PA, there are several
objective measures of PA which cannot easily estimate SB (i.e., pedometers and heart rate monitors). Unlike the measurement of PA, wherein energy expenditure above a threshold of 1.5 METs is indicative of PA, SB refers to any activity which is performed from the seated or lying position while awake. Hence, the precise objective measurement of SB also requires information about body position, which can be detected through inclinometry [8, 88]. Not all SB measurement tools are capable of determining body position, and thus these measures only estimate SB based on energy expenditure (either measured directly, or indirectly estimated from accelerometer-based devices; Figure 1.9). However, there is no SB measurement tool currently capable of accurately estimating body position and energy expenditure concurrently; measurement tools capable of estimating body position are thus only able to classify time spent sitting, lying down, or standing.

Throughout my thesis, I have measured SB using the MW8 and the SWA. Each of these measures has evidence of validity and reliability for estimating older adult SB [136, 137, 140, 141], however neither device is capable of estimating body position.

1.3.2.3 Current evidence examining the impact of sedentary behaviour on older adult cognitive health

In comparison to the current level of evidence examining the impact of PA and exercise on older adult cognitive health, far less is known about how SB can impact older adult cognitive health. Nonetheless, I will review the current evidence on how SB can impact cognitive health.

There are two reviews which have suggested SB may be associated with poorer cognitive function and increased risk of cognitive impairment [6, 7]. These reviews suggest SB may 1) negatively
Figure 1.9 Measures of sedentary behaviour and their classifications

- Subjective Measures
  - Behavioural Measurement
    - Diaries Logs
    - Surveys Questionnaires
    - EMA
  - Objective Measures
    - Biomechanical Measurement
      - Inclinometers
      - Accelerometers
    - Thermodynamic Measurement
      - Multimodal Sensors
      - Direct Observation
      - Calorimetry

Legend:
- Blue: Estimates body position
- Orange: Estimates energy expenditure

EMA: Ecological momentary assessment
impact the cellular mechanisms by which PA and exercise training impact cognitive health; and 2) alter the connectivity of the brain such that there is a negative impact on cognitive function. The authors of these reviews are quick to point out that epidemiological data are needed to confirm this preliminary evidence [6, 7].

Very little is known about the epidemiology of SB. Most of the evidence surrounding the effects of SB on neurophysiology is based on the control condition of exercise trials [261]; however, SB is not just the inverse of exercise or PA. Preliminary epidemiological evidence does suggest SB is associated with poorer cognitive function and a plausible mechanism is emerging by which SB is associated with cognitive decline [6, 7]. Recent data suggest prolonged sedentary time impairs glucose and lipid metabolism [88], which are both recognised as risk factors for cognitive decline and all-cause dementia [262, 263]. Only one study to date has examined the relationship between SB and brain health [264]. The authors found that higher amounts of self-reported SB were associated with decreased medial temporal lobe thickness. There is also evidence that SB is related to cognitive decline by analogy; SB is associated with many chronic diseases [265-267], which are also associated with cognitive impairment and dementia risk [268-270].

To my knowledge, there have been no RCTs conducted to examine whether reducing SB can impact older adult cognitive health. While this type of investigation is of interest, given that it is still unclear whether SB is associated with reduced cognitive function, the conducting of RCTs may need to wait until there is enough epidemiological evidence to suggest reducing SB could improve older adult cognitive health.
1.3.2.3.A  Mechanism by which sedentary behaviour impacts cognitive health

Much is also still unknown about the mechanism by which SB impacts cognitive health. At the present time, it is unclear how SB may cause changes in brain volume and functional connectivity. In addition, it is still unclear which areas of cognitive function are specifically affected by changes in SB. Two reviews have suggested SB may impact cognitive health by 1) negatively impacting the cellular mechanisms by which PA and exercise training impact cognitive health; and 2) altering the connectivity of the brain such that there is a negative impact on cognitive function [6, 7]. A more recent review by Wheeler and colleagues [271] posited that SB influences cognitive health by negatively impacting glycemic control. This hypothesis seems somewhat promising since SB is indeed linked to reduced glucose sensitivity [272], and poorer glycemic control is linked to poorer cognitive health [273]. However, there are no data to confirm this hypothesized mechanism.

1.3.2.4 Summary of the current evidence for how sedentary behaviour can impact older adult cognitive health

There is only preliminary evidence at this time that SB impacts older adult cognitive health [6, 7, 271]. Research is still needed to determine whether there is a relationship between increased SB and poorer cognitive function in later life. These data would be beneficial in determining whether interventions to reduce SB—and thus improve cognitive health—may be worth pursuing. The mechanism by which SB impacts cognitive health is also unclear at this time.

1.3.3  Sleep and older adult cognitive health

1.3.3.1 Defining sleep
Sleep is defined as a rapidly reversible state of immobility and greatly reduced sensory responsiveness [274]. An important further criterion is that sleep is homeostatically regulated, whereby lost sleep is made up with an increased drive for sleep and a consequent “sleep rebound”. Sleep is also a behavior whose presence, quality, intensity and functions vary between species and across the lifespan. Some animals (including humans and most other primates) use sleep to maximize energy savings by reducing body and brain energy consumption, releasing hormones, and conducting a variety of recuperative processes—all of which are accomplished by finding a safe sleeping site that does not offer threat of predation [274-276]. Some species appear to be able to accomplish these processes during the waking state [277, 278]. Sleep is therefore not a universal state with the same underlying function in all species [279, 280], and human sleep is thus distinct.

Science has long recognized that human sleep is a distinct physiological and psychological phenomena (Figure 1.10; [281, 282]). Physiological sleep are the distinct physiological processes and structure of sleep (i.e., sleep architecture; [87]). The physiological processes of sleep include hormone regulation, recuperative processes, and all other physiological processes that occur during sleep in the central nervous system (CNS) and the periphery. There are two structural types of sleep: non-rapid eye-movement (NREM) and rapid eye-movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4 (or 3 stages in some more recent classification systems), representing a continuum of relative depth. Stages 3 and 4 are classified as slow-wave sleep (SWS), or deep sleep, and are also used as a marker of sleep depth and sleep quality [283]. Psychological sleep is the 1) perceptions and attitudes (e.g., anxiety, fatigue, etc.); 2) behaviours and habits (betime routines, sleep patterns, etc.); and 3) mental characteristics (mood states, psychological traits, mental disorders, etc.).
Figure 1.10 Dimensions of sleep and their associations
Each component of physiological sleep (i.e., physiological processes and sleep structure) is tightly linked, and centrally controlled by the brain [87, 281, 282]. The individual components of psychological sleep are also related to each other, and physiological and psychological sleep are also dynamically associated with each other. An example of this complex interrelationship can be understood within the contexts of chronic insomnia [284]. Chronic insomnia can occur due to physiological processes (e.g., hormonal imbalances) which can alter sleep architecture due to shortened sleep cycles. These changes in sleep physiology can also affect perceptions around sleep, as well as lead to long-term changes in mood states and psychological traits. Conversely, psychological sleep changes due to anxiety and/or other external stressors can lead to changes in behaviour and perceptions of sleep, as well as changes in the physiological nature of sleep.

The term *sleep quality* is also widely used by researchers, clinicians, and the public in reference to how well a person sleeps (both physiological sleep and psychological sleep); however, the term sleep quality is vague and has lacked definitional consensus until recently. The National Sleep Foundation has recently defined several aspects of sleep quality including: 1) *sleep efficiency* (i.e., ratio of time spent sleeping to time spent trying to sleep); 2) *sleep latency* (length of time in minutes it takes to transition from wake to sleep); 3) *sleep duration* (total time spent sleeping); 4) *awakenings* (number of times a person wakes after imitating sleep); 5) *wake after sleep onset* (WASO; the time spent awake after sleep has been initiated and before final awakening); and 6) sleep architecture [283]. Given that each of these markers of sleep quality can impact health, I define sleep quality as the distinct attributes of sleep that impact health and well-being.
Sleep quality is both objective and subjective (Figure 1.11; [285]). *Objective sleep quality* can be classified according to the physiological aspects of sleep, while *subjective sleep quality* is based on how an individual feels about their sleep and can thus reflect both physiological and psychological sleep. Importantly, older adults’ objective sleep quality is poorly correlated to their subjective sleep quality [286], suggesting that objective and subjective sleep quality provide different information about older adult sleep.

**Figure 1.11 Objective and subjective quality and their relationships to the dimensions of sleep**

![Diagram of circadian rhythms and sleep quality](image)

Sleep and sleep quality are also inextricably linked to the function of circadian rhythms. Briefly, *circadian rhythms* are ~24-hour cyclic changes in physiology and behavior that are governed by various biological clocks which coordinate the sleep-wake cycle with the solar light-dark cycle [287-289]. Key features of circadian rhythms include the synchronizing effect of light-dark cycles, persistence of the rhythmicity in constant darkness, and negative masking by light, leading to
rhythmic behaviour even in an animal that lacks the ability to maintain rhythms in constant conditions. This rhythmic behaviour in the presence of a rhythmic environment highlights the difference between a rhythm which is endogenously generated, and one which is set by the environment [290]. Rhythms that are observed in a rhythmic environment are referred to as diurnal (i.e., daily) rhythms and, thus, normal human circadian rhythms are diurnal.

The process by which the biological clock is synchronized with the solar light-dark cycle (i.e., entrainment) is controlled by the suprachiasmatic nuclei (SCN), which is located directly above the optic chiasm in the hypothalamus of the brain [291]. Under normal conditions, the SCN functions as “the master biological clock” of the CNS and interacts with the homeostatic recovery process that increases sleep need as a simple function of prior wakefulness with the function of the circadian clock. The entrainment of the biological clock is accomplished through certain external stimuli, known as zeitgebers (from the German time-givers). These time-givers help to prevent inadvertent drifting or divergence of the biological clock from the 24-hour day. Zeitgebers can be used as a chronobiotic—that is, a therapeutic agent to help realign the biological clock with the solar light-dark cycle. I will discuss two chronobiotics in detail in Section 1.5.2.3: light and activity.

1.3.3.2 Sleep and circadian rhythms measurement

1.3.3.2.A Measuring sleep

Sleep is thus a complex physiological and psychological phenomena [87, 281], and the precise measurement of sleep in humans is challenging. As with PA and SB, sleep can be measured objectively and subjectively. Given that objective measures of sleep index the physiological
aspects of sleep, there are two distinct dimensions of sleep which are assessed using objective measurement. *Physiological measurement* provides information about the distinct physiological processes and architecture of sleep. *Biomechanic measurement* provides information about the movement of the body during sleep, and can be used to estimate sleep quantity and quality. Subjective measures can be used for understanding the dimension of *psychological and behavioural measurement*—that is, the distinct behaviours, perceptions and characteristics of sleep and sleep quality. Objective and subjective measures of sleep thus measure different components of sleep; hence, there is no best measure for assessing sleep (Figure 1.12). The precise measurement of sleep also requires that measures of sleep have evidence of validity and reliability, are population specific, and are sensitive to change.

The criterion measure for measuring objective sleep and sleep quality is polysomnography (PSG) [292]. PSG monitors a number of physiological processes while a subject is sleeping including brain activity (i.e., EEG), eye movements, muscle activity, heart rate, breathing functions (respiratory air flow and respiratory effort), and pulse oximetry. PSG can thus provide information about sleep architecture, sleep related breathing, and other markers of sleep quality. While PSG thus provides accurate, reliable, and sensitive information about a person’s sleep, PSG is expensive, time-consuming, and requires significant participant and researcher burden. Indeed the invasive nature of PSG—usually requiring an overnight stay in a sleep laboratory or clinic—makes long-term multi-night recordings impractical.

Estimating sleep quality using wrist-worn actigraphy is an increasingly popular alternative for objectively-measuring sleep quality, especially since these devices can be used to observe multiple
Figure 1.12 Measures of sleep and their classifications

Objective Measures

Biomechanical Measurement

Physiological Measurement

Subjective Measures

Psychological and Behavioural Measurement

Diaries Logs | Surveys Questionnaires | EMA | Accelerometers | Multimodal Sensors | Direct Observation | Apnea Hypopnea Index | EEG | Polysomnography

Low Cost

Low Sensitivity

High Cost

High Sensitivity

Legend | Estimate sleep structure

EMA: Ecological momentary assessment
days of sleep under normal daily-living conditions. Wrist-worn accelerometers have also been validated for measurement of sleep parameters by comparison with PSG [293], and thus actigraphy is currently accepted as a valid, practical alternative to PSG, allowing for long-term continuous sleep assessments at home [294, 295]. While wrist-worn actigraphy does provide valid estimates of sleep, it is open to issues of validity and reliability compared to PSG—especially among individuals with chronic insomnia [296]. Wrist-worn actigraphy also does not provide information about sleep architecture. Sleep can also be objectively estimated using multimodal sensors [297], however these devices provide slightly less accurate estimates of sleep than wrist-worn actigraphy—likely because multimodal sensors cannot detect small subtle changes in movement that may indicate wakefulness. Like wrist-worn actigraphy, multimodal sensors cannot provide information about sleep architecture.

Throughout my thesis, I measured objective sleep using the MW8 wrist-worn actigraph. The MW8 has preliminary evidence of validity for estimating sleep [298]. I have also recently examined the number of days needed to reliably estimate sleep using the MW8 (under minor revision in Sleep Science and Practice, Appendix B); the data appear to indicate that ≥7 days of monitoring can provide estimates of sleep with evidence of reliability. Sleep can also be measured objectively using the SWA [297], however none of my thesis studies measured sleep using this device.

Sleep can also be measured using subjective methods such as diaries and questionnaires. Importantly, subjective measures of sleep likely measure different aspects of older adult sleep than objective measures [286]. Subjective measures of sleep are quick and easy to administer and score, and can discriminate “good” vs. “poor” sleepers, but they are not able to detect subtle but clinically
important changes in sleep quality due to age or disease. Throughout my thesis studies, I have measured sleep subjectively using the Pittsburgh Sleep Quality Index (PSQI; [299-301]) as well as the consensus sleep diary (CSD; [302]); each of these instruments has evidence of validity and reliability for measuring older adult subjective sleep quality.

1.3.3.2.B Measuring circadian rhythms

The precise measurement of circadian rhythms is perhaps even more challenging than measuring sleep. Circadian regulation can be indexed using objective and subjective methods of measurement, and there are broadly three dimensions of circadian rhythms that can be measured in humans (Figure 1.13). Physiological measurement examines the physiological markers of circadian physiology (e.g., melatonin levels, core body temperature, etc.), while biomechanical measurement indexes the activity and movement of an individual as a less invasive and burdensome method for estimating circadian regulation; each of these methods are objective. Behavioural measurement provides information about circadian-related behaviour using subjective methods. Each of these measures has benefits and drawbacks and thus there is no single best measure for assessing circadian regulation.

Perhaps the gold standard for measuring circadian physiology is the use of physiological markers at multiple time points throughout a day(s) [288, 303]. These data can provide precise information about an individual’s daily circadian rhythm. However, the ~24-hour diurnal fluctuations of circadian rhythms makes field-measurements of circadian markers extremely difficult. Indeed, most studies of circadian physiology are lab-based studies wherein biomarkers of circadian physiology are measured (i.e., core body temperature, melatonin levels, cortisol, etc.; [288, 303]).
Figure 1.13 Measures of circadian rhythms and their dimensions

- **Subjective Measures**
  - Behavioural Measurement
    - Diaries Logs
    - Surveys Questionnaires
  - Biomechanical Measurement
    - Accelerometers
    - Multimodal Sensors?
  - Physiological Measurement
    - Cortisol
    - Melatonin
    - Core Body Temperature

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**Low Cost**

**Low Sensitivity**

---

**High Cost**

**High Sensitivity**
Some aspects of circadian regulation can also be measured biomechanically using actigraphy (most commonly wrist-worn actigraphy), whereby fluctuations in activity are used to estimate differences in circadian rhythms [304]. However, these measures are crude estimates of circadian timing, and cannot easily determine different phases in the circadian rhythm. Moreover, the sensitivity of these measures to change over time is unknown. It might also be possible to measure circadian rhythms using multimodal sensors such as the SWA, however no such tool has been developed to my knowledge.

Lastly, subjective questionnaires can provide some information about circadian regulation. Several questionnaires exist which can provide some information about an individual’s circadian behaviour, most specifically their chronotype—or the timing of a person’s sleep-wake cycle with the solar light-dark cycle [305-307]. However, these data are prone to self-report bias and cannot provide information about whether an individual is experiencing circadian dysregulation or is merely an early- or late-riser. It is also unclear whether these types of measures can be used to measure changes in circadian regulation over time. Given the challenges and limitations of measuring circadian regulation using field-based methods, I did not include any measures of circadian regulation as an outcome of interest in my thesis studies.

1.3.3.3 Sleep and circadian rhythms in normal aging

The principal entraining zeitgeber for the human biological clock is light [308, 309], exerting its influence on retinal ganglion cells containing melanopsin [310-313]. Retinal light exposure directly stimulates the activity of the SCN, which phase delays the biological clock such that the desire for sleep decreases and wakefulness increases (or is maintained); reduced retinal light
exposure results in less activity of the SCN and increases the desire to sleep by phase advancing the biological clock [291]. Thus, under normal circumstances, the biological clock is entrained to the solar light-dark cycle through the regulation of the SCN—which helps maintain a regular sleep-wake cycle [314].

However, aging significantly alters the functioning of circadian rhythms. Aging is associated with the biological clock initiating sleep-promoting mechanisms earlier in the day [315, 316], and a decreased amplitude in circadian signals, which increase sleep need [317, 318]. This weakening of circadian regulation with aging likely plays a prominent role in the fragmentation of sleep-wake rhythms observed in older adults during 1) the wake maintenance zone, which occurs 2-3 hours before habitual bedtime; and 2) the sleep maintenance zone, which occurs 2-3 hours before habitual wake time [2]. In addition, older adults have reduced sensitivity to light due to age-related loss of retinal ganglion cells and axons [319], which leads to poorer functioning of the SCN and divergence of the biological clock from the solar light-dark cycle [320]. Behavioural changes in older adulthood—such as spending less time outdoors—could also further decrease bright light exposure, which may be a contributing factor to the decreased amplitude of circadian rhythms [2].

This age-associated weakening in circadian regulation may also be linked to declines in sleep quality in older adulthood. Sleep changes as a function of normal aging, both in terms of decreased quality and quantity [321, 322]. More than half of adults over 65 years report at least one chronic sleep complaint—the most common complaints being the inability to stay asleep at night, and excessive daytime sleepiness resulting in frequent daytime naps [323]. These complaints, in particular the reports of excessive daytime sleepiness (a key indicator of accumulated sleep debt
suggest that age-related changes in sleep are likely the result of something beyond reduced need for sleep. The evidence therefore suggests that: 1) normal aging may disrupt the function of circadian rhythms; and 2) these age-related changes in the functioning of circadian rhythms may explain the declines in both sleep quality and quantity as people age.

1.3.3.4 Sleep, circadian rhythms, and older adult cognitive health

The effects of poor sleep on cognitive health and functions are apparent following both acute and chronic poor sleep [326]. Neurocognitive impairments following acute sleep loss are experienced almost universally, and include impairments in attentional processing, executive function, memory, as well as emotional regulation and sensory perception [327-330]. Importantly, optimal cognitive functioning is integral for older adult quality of life since it is linked to physical function and independence [331, 332], emotional regulation [333, 334], and even eating behaviour [335]. Attentional failures or lapses due to sleep loss are considered the primary causative factor underlying fatigue-specific automobile accidents [336, 337], with a level of psychomotor impairment seen following acute sleep loss similar to that observed during alcohol intoxication [338]. Perhaps most importantly, the observed neurocognitive impairments which are a consequence of poor sleep can be attributed to sub-optimal functioning of the prefrontal cortex [326], which is the principle cortical area responsible for higher-level cognitive processes [339, 340].

While it is clear that poor sleep quality can have an immediate impact on cognitive health, the chronic effects of poor sleep can have even more sinister consequences. Indeed, poor sleep quality is recognized as an important predictor of AD [341]. Older adults diagnosed with obstructive sleep
apnea (OSA)—a common chronic sleep disorder characterized by frequent episodes of upper airway collapse during sleep, which results in recurrent arousals from sleep [342]—convert to MCI and AD at a younger age [343]. However, successfully treating OSA can delay the age of MCI onset [343], and improve cognitive function among adults with AD [344]. Poor sleep is also more prevalent among individuals with cognitive impairment as compared to their cognitively healthy peers [345], and epidemiological evidence indicates that poor sleep quality is associated with an increased risk of progression from MCI to dementia [346].

Poor sleep can also contribute to AD pathophysiology, and disruptions in sleep quality and circadian alignment represent typical AD biomarkers. Circadian dysregulation is also one of the hallmarks of AD progression [2]. In fact, sleep disruptions that occur in AD are often exaggerated in a way that implies a form of accelerated or hyper-aging [347], such that fragmentation of sleep-wake rhythms in adults with AD is more akin to much older adults without AD. Moreover, the SCN of older adults with AD is significantly atrophied compared to their cognitively healthy peers, which likely contributes to the fragmentation of sleep-wake cycles in AD [348-350]. Increases in cortical Aβ leads to increases in sleep fragmentation and disrupts diurnal rhythms in the APPswe/PS1δE9 mouse model of AD [351]. Chronic sleep restriction and corresponding increases in wake-time significantly escalates Aβ accumulation in transgenic Tg2576 mice [352]. Increased Aβ load is linked to disrupted NREM slow-wave sleep (i.e., stages 3 and 4) and impaired hippocampal-related memory consolidation [353]. A recent experiment randomly assigned healthy middle aged men to either 1 night of total sleep deprivation or their normal sleep routine [354]; the results indicated that 1 night of sleep deprivation significantly increased cerebrospinal fluid levels of Aβ. A separate PET study showed that acute sleep deprivation over one night increased
Aβ burden in brain regions implicated in AD [355]. It therefore appears that a vicious cycle of accelerating AD progression may occur with poor sleep—wherein poor sleep quality causes an increase in AD progression, and vice-versa [9].

While poor sleep thus appears to contribute to cognitive decline and dementia progression, good quality sleep appears to be neuroprotective. For example, NREM sleep promotes the clearance of Aβ that accumulates during wake-time [356], and combats oxidative stress (which is linked to AD pathology) by enhancing cellular restitution processes [9]. Improving sleep quality may also be an especially potent therapy for populations with a high risk for dementia, such as populations with the APOE-ε4 allele, who exhibit significant sleep deficits [357]. Given that sleep is a modifiable behaviour which can target multiple cognitive processes [358-360], promoting older adult sleep appears to be an important strategy for maintaining cognitive health in later life.

1.3.3.5 Summary of the current evidence for how sleep and circadian rhythms can impact older adult cognitive health

There is thus a growing body of evidence that indicates sleep and circadian regulation are dynamically related to cognitive health. However, it is not yet clear whether improving sleep and circadian regulation can also improve cognitive health. It is also unclear whether improving circadian regulation can improve the sleep of older adults at risk for dementia.

1.3.4 Summary of the current evidence for how each time-use activity behaviours impacts older adult cognitive health
Current evidence thus indicates that PA, SB, and sleep may each play a critical role in maintaining older adult cognitive health. Evidence from animal models, observational studies, and RCTs indicates that PA (especially PA in the form of exercise training) can promote older adult cognitive health. Less is clear about how SB can impact older adult cognitive health, however preliminary evidence suggests that it may be associated with cognitive decline. Sleep appears to be critical for healthy cognitive aging, although it remains to be determined whether improving sleep promotes cognitive health.

1.4 The dynamic relationships of time-use activity behaviours and circadian rhythms with older adult cognitive health

1.4.1 Concurrent measurement and analysis of multiple time-use activity behaviours and/or circadian rhythms

There are a few methods available for measuring PA, SB, and sleep concurrently. Presently, available methods include actigraphy, multimodal sensors, and systematic direct observation. Irrespective of the method used to capture all three time-use activity behaviours concurrently, only limited aspects of each behaviour can be estimated. For example, none of these methods can capture the psychological and behavioural aspects of sleep, and thus there is no single best measure for capturing all time-use behaviours concomittantly.

A field-method capable of capturing time-use activity behaviour within the context of the circadian cycle is not currently available. While wrist-worn actigraphy (in particular the MW8) is capable of approximating the circadian rest-activity cycle and measuring each time-use activity behaviour
[136, 298, 304], there is not currently an analytical framework for measuring time-use activity behaviour within the context of the circadian cycle. This is perhaps because circadian rhythms are a set of physiological processes that have little ability for self-determination [12, 288, 307, 317]; on the other hand, time-use activity behaviours are at least to some extent a choice. For example, an individual cannot control diurnal changes in melatonin and cortisol, however they can decide whether to go for a walk, watch television, or go to bed earlier (or later).

Some approaches have been suggested for analyzing the contribution of each time-use activity behaviour to health. One approach is isotemporal substitution analysis, which simultaneously models the specific activity being performed and the specific activity being displaced in an equal time-exchange manner (e.g., the impact of exchanging 1 minute of PA for 1 minute of SB, or vice-versa; [361]). Pedišić and colleagues [3, 362] recently argued for the use of compositional data analysis for examining the contributions of each time-use activity behaviour to health. In this approach, time-use activity behaviour is considered to be a composition matrix and can be analyzed according to the clustering of time-use activity behaviours at different times throughout the 24-hour day.

However, as I have highlighted above, each time-use activity behaviour is complex and multi-dimensional. Time-use allocation is not the only factor which must be considered in the analyses of these behaviours. For example, it is unlikely that 9 hours of poor sleep (i.e., low sleep efficiency, minimal stage 3 and 4 sleep, etc.) is somehow better than 7 hours of high quality sleep. It therefore seems that at the present time such analysis techniques are ill-fitted to elucidating the combined role of PA, SB, and sleep on older adult cognitive health. Furthermore, a long-standing principle
of scientific philosophy has been that of scientific economy—that is, complexity should not be assumed unnecessarily [363]. In this instance, I argue that examining the interactions of complex biological phenomena such as time-use activity behaviours using mathematically complex models which are difficult to interpret and/or require assumptions about the equal importance of a variable (i.e., time) seems an ill-fitted method to understanding how time-use activity behaviours can impact older adult cognitive health. Instead, I suggest that using the general linear model (GLM) can provide a simple, easily interpretable, and well-understood structure by which researchers can untangle how PA, SB, and sleep impact older adult cognitive health.

1.4.2 Current evidence on the dynamic relationships between time-use activity behaviours and older adult cognitive health

Epidemiological studies have consistently found people with greater PA report sleeping better compared to more sedentary individuals [11]. While the reason for why PA and sleep are related is still unclear, current evidence suggests three possible explanations [364, 365]. First, negative affective states (i.e., depressive symptoms and anxiety) contribute to poor sleep [366], and PA counters this via its antidepressant and anxiolytic effects [367, 368]. Second, obesity is related to poorer sleep quality [369], and PA has a direct impact on weight regulation which may promote better sleep [370]. Third, regular PA improves or maintains physical function [371]; poor physical function is associated with poorer sleep quality in older adults [372]. However, much of the evidence to date is based on self-reported PA and self-reported sleep [11, 365], which can be quite different from objectively-measured data [286, 373]. Of final importance, there is at least preliminary evidence that the relationship between PA and sleep may be bi-directional [374].
The relationship between PA and sleep quality may weaken with age [375]. One potential reason for this functional weakening is that we simply need less sleep as we age [376]. In addition, there is some evidence that underlying changes in older adult neurobiology (e.g., neural atrophy, nocturnal hypoxia, neuroendocrine changes, and altered neuromodulation) may reduce the potential to impact sleep quality through strategies such as PA [296].

Although there is ample evidence that both PA and sleep quality can impact older adult cognitive health, together with a growing body of evidence suggesting that PA is associated with better sleep quality, it is unclear whether PA and sleep impact cognitive health through divergent or convergent mechanisms. Recent evidence suggests that sleep efficiency may mediate the relationship between PA and cognitive function [377]; these results provide at least initial support for the restoration hypothesis, which suggests that energy expenditure (i.e., PA) stimulates a restoration process by which sleep allows the body and brain to recuperate [364].

By comparison, little is known about how SB can impact older adult sleep. A systematic review and meta-analysis of 16 studies of adults aged 18+ years indicated that higher SB was associated with an 18% and 38% increased risk for insomnia and sleep disturbances, respectively [378]; however, only 3 studies of adults over 55 years of age were included in this review. Other recent investigations among older adults also suggest SB may impact sleep. Madden and colleagues [379] determined that higher objectively-measured SB was associated with reduced objectively-measured sleep efficiency among community-dwelling older adults. Kline and colleagues [380] also found that older adults who engaged in greater amounts of self-reported SB had an increased risk of PSG-determined sleep disordered breathing. Seoul and colleagues [381] determined that
higher SB was associated with poorer PSQI score. Interestingly, a recent cross-sectional investigation among older adults with dementia in a long-term care facility determined that while participants were highly sedentary, they also obtained ~7 hours of sleep each night [382]. It is thus unclear how SB may impact older adult sleep, although preliminary evidence suggests that SB may have deleterious effects on sleep.

Few studies have also examined how PA and SB are associated with each other in older adulthood. A systematic review of observational studies examining the relationships between PA and SB in adults 18+ years found a negative association between PA and SB [10]. However, most of this evidence is based on self-reported PA and self-reported SB, and only one study examined these associations in middle- and older-adulthood exclusively [383]. More research is thus needed to examine how the relationships between PA and SB patterns change in older adulthood.

1.4.3 Current evidence on the dynamic relationships between time-use activity behaviours and circadian rhythms

PA in the form of exercise training appears to have chronobiotic effects in humans [320, 384, 385]. The chronobiotic properties of PA have been well established in various animal models, with wheel running being the most commonly used approach in rodents [386, 387]. Briefly, the circadian rhythms of rodents can be entrained by regularly scheduled exercise [388, 389], and single episodes of running in novel running wheels can advance the circadian clock [386, 390], while presentation of a novel running wheel can accelerate re-entrainment and induce single phase advances as large as 12 hours [391]. However, human studies on the chronobiotic properties of PA are difficult, given the challenges associated with isolating the effects of exercise from other
factors such as light, food, and social influences [392, 393]. However, studies of blind people who lack sensitivity to light—but remain able to entrain to daily work/social schedules without the involvement of exogenous melatonin—suggest that non-photic stimuli are capable of synchronizing circadian rhythms [393]. It has yet to be determined whether it is PA, social influences, regularly scheduled mealtimes, or a combination of these (and possibly other potential zeitgebers), which provides the critical entrainment signal.

While the effects of PA as a chronobiotic have yet to be fully established, PA does appear to have a specific phase-response curve [393]. Briefly, PA performed in the morning or early afternoon does not appear to have a consistent effect on phase shifts of the biological clock; however, engaging in PA in the late afternoon causes a modest phase advance of the biological clock, while late night PA causes a modest phase delay of the biological clock [384, 385]. Importantly, the effects of PA as a zeitgeber have been found in both young adults and older adults [385]. The time-based response to how PA can impact the SCN is hypothesized to coincide with the timing of the opening of the “sleep gate”—the shift of the biological clock from generating a waking signal, which reduces sleep need, to generating a signal that facilitates sleep [12].

Very little is known about how SB may impact circadian regulation. A recent randomized cross-over study of young men (N= 16) found that a 24-hour sedentary protocol (i.e., <1,000 steps) lead to significant reductions in circadian rhythm amplitude compared to a 24-hour PA protocol (>15,000 steps) [394]. However, this appears to be the first analysis wherein the impact of SB on circadian regulation was examined.
1.4.4 Summary of the current evidence examining the relationships between time-use activity behaviours, circadian rhythms, and cognitive health

Increasing older adult PA, reducing SB, and improving older adult sleep and circadian regulation appear to be viable strategies for maintaining older adult cognitive health. There is growing evidence that PA can positively impact older adult sleep and circadian alignment, and there is at least preliminary evidence that PA and sleep may improve cognitive health through multiple mechanisms—both convergent and divergent. However, little is known about how SB can impact older adult sleep and circadian regulation, and it is currently unknown whether SB impacts sleep through a convergent or divergent mechanism from PA.

1.5 Current strategies to promote older adult physical activity, reduce sedentary behaviour, and improve sleep and circadian rhythms

In this section, I will provide a brief review of the methods for promoting each time-use activity behaviour. In-depth reviews of current methods for promoting PA [395, 396], reducing SB [397], and improving sleep [398-400] can be found elsewhere. I will instead review the methods I used for promoting PA and SB in my thesis (Section 1.5.1), as well as provide a brief discussion about the current methods for promoting older adult sleep and circadian regulation (Section 1.5.2).

1.5.1 Strategies to promote physical activity and reduce sedentary behaviour

There are a wide variety of evidence-based methods for promoting PA and reducing SB [395-397]. While each of these methods may help to improve PA and SB, there is not a universal best method for promoting PA and SB change. Indeed, there is no silver bullet for promoting PA and reducing
SB, and if there were, one would expect that researchers would be much closer to solving the global pandemic of low PA and high SB [401].

One method for promoting PA and reducing SB is the Brief Action Planning (BAP) approach [402]. BAP is a highly structured, stepped-care, self-management support technique which is grounded in the principles and practice of motivational interviewing—a therapeutic technique designed to enhance an individual’s motivation to change behaviours and guide him or her into action (Figure 1.14; [403, 404]). BAP can be used to facilitate goal setting and action planning to build self-efficacy about PA and SB (Figure 1.16; [405-407]).

As described in Figures 1.14 and 1.15, the initial consultation using BAP involves asking three questions about an individual’s PA and then focusing on building five skills. The questions asked are meant to elicit talk about behaviour change, while the skill building opportunities are used to determine strategies which will help the person reach and obtain their behaviour change goals. During follow-up consultations, the individual is asked whether they reached their behaviour change goals, and then modifications to the goals are made accordingly.

While BAP is an evidence-based strategy for promoting PA and SB, there are some disadvantages to the use of the technique to promote PA and reduce SB. Most importantly, BAP is individually-focused; the patient (or research participant) is asked questions about whether or not they want to increase their PA and reduce their SB. According to the theory of planned behaviour [408], an individual will not change their behaviour without: 1) motivation; and 2) perceived behavioural
Figure 1.14 Overview of the Brief Action Planning Approach during initial and follow-up consultations

Initial Consultation

Follow-up Consultations
Figure 1.15  Brief Action Planning Approach for A) promoting physical activity and B) reducing sedentary behaviour
control. If a person does not have the motivation for behaviour change, or thinks their behaviour is beyond their control, then changes to behaviour are highly unlikely. BAP may thus require multiple sessions in order to elicit talk about changing PA and SB habits. The implementation of BAP also requires extensive time on the part of the counselor and the patient. Indeed, a minimum of 20-minutes is suggested during the initial consultation [402], and bi-weekly follow-up sessions also require an agreed upon time and place for the counselor and patient to discuss the implementation of the action plan. These challenges to the implementation of BAP make it difficult for the intervention strategy to be implemented on a large-scale; however, small-scale, individually-based implementations of BAP can be highly successful for promoting PA and reducing SB [405-407].

Another strategy for promoting PA and reducing SB is consumer-available, wearable activity-monitoring technology. These devices present several distinct advantages as a PA promotion and SB reduction tool including: 1) adults typically perceive activity-monitors as useful [409]; 2) these devices incorporate multiple behavioural change strategies [410]; and 3) clinicians can readily use these devices to help promote behaviour change among their underactive patients [411]. While the use of these devices alone might not be enough to induce behaviour change [412], the delivery of BAP to promote PA and reduce SB might be enhanced by implementing wearable activity-monitors [145].

1.5.2 Strategies for improving sleep and circadian rhythms

There are a number of methods available for improving sleep quality. Broadly, these can be classified as pharmacological and non-pharmacological. Pharmacological interventions to
improve sleep are outside the scope of my thesis and have been reviewed elsewhere [413, 414]. There are three methods of promoting sleep which I will now briefly review: 1) cognitive behavioural therapy, with a special emphasis on sleep hygiene education (Section 1.5.2.1); 2) PA and exercise training (Section 1.5.2.2); and 3) chronotherapy (Section 1.5.2.3).

1.5.2.1 Cognitive behavioural therapy and sleep hygiene education

Cognitive behavioural therapy (CBT) is a powerful tool for promoting better sleep quality [284, 415-417]. Broadly, CBT is a psychological treatment designed to break patterns of maladaptive thinking and behaviour. The treatment consists of a behavioural component (stimulus control, sleep restriction, and relaxation techniques) combined with cognitive strategies (managing sleep-related worries, racing mind, and intrusive thoughts) and education (sleep hygiene). Meta-analyses indicate that CBT has moderate-to-large and durable effects on subjective sleep quality, and objective sleep efficiency, latency, and WASO; the effects of CBT on sleep are also comparable in size to pharmacological therapies [418-420].

As highlighted above, one aspect of CBT is sleep hygiene education. Sleep hygiene is a set of behavioural practices that can impact sleep quality, such that poor sleep hygiene can exacerbate or even cause poor sleep, while good sleep hygiene results in feeling more rested and alert upon awakening [421-423]. Sleep hygiene education thus teaches strategies which can enhance sleep (e.g., not watching television before bed, bedtime habit formations, or avoiding the bedroom unless one is tired and ready to sleep). It is also hypothesized that sleep hygiene might be a useful tool for promoting other behaviours which can impact sleep quality and circadian regulation—such as light exposure and PA [424].
Although sleep hygiene education is currently one of the recommended strategies for promoting better sleep [425], there is insufficient evidence at this time to suggest that sleep hygiene education alone can improve sleep [421]. Current recommendations therefore suggest that sleep hygiene should be used in conjunction with other therapeutic approaches for enhancing sleep [426].

1.5.2.2 Physical activity and exercise training

As discussed in Section 1.4.2, there is a growing body of evidence which indicates that PA and exercise training may each positively impact older adult sleep [427, 428]; however, it seems that the effects of PA and exercise training weaken with age [365]. While it is thus unclear whether promoting PA or exercise training should be the frontline approach for older adults experiencing poor sleep, current recommendations suggest that daytime PA and exercise training may help enhance sleep quality [429]. The precise prescription of PA and exercise training for promoting sleep is also currently unclear [11, 365]; specifically, the precise frequency, intensity, type, or duration of PA and exercise training which is most beneficial for promoting sleep. As I will discuss in Section 1.5.2.3.B, timed PA and exercise training can also be used in chronotherapy to promote sleep.

1.5.2.3 Chronotherapy

Chronotherapy refers to a set of intervention strategies that use effectively timed zeitgebers in order to realign the biological clock with the solar light-dark cycle [2, 430]. There are a number of different zeitgebers which can entrain the biological clock including light, food, PA and exercise training, and social influences [291, 392, 393]. I will discuss the use of two potential
chronotherapeutics which I used in my thesis studies: 1) bright light therapy (BLT; Section 1.5.2.3.A); and 2) PA and exercise training (Section 1.5.2.3.B).

1.5.2.3.A Bright light therapy

The principal entraining zeitgeber for the human biological clock is light [308, 309], which exerts its influence on retinal ganglion cells containing melanopsin [310-313]. Retinal light exposure directly stimulates the activity of the SCN (Figure 1.16), causing a suppression of melatonin production which phase delays the biological clock such that the desire for sleep decreases and wakefulness increases (or is maintained); reduced retinal light exposure results in less activity of the SCN (and less melatonin production) and increases the desire to sleep by phase advancing the biological clock [291]. While the importance of light is thus integral for the proper function of the SCN and the biological clock, older adults have reduced sensitivity to light which leads to poorer function of the SCN and divergence of the biological clock from the solar light-dark cycle [320]. Behavioural changes in older adulthood—such as spending less time outdoors—can also further decrease bright light exposure, which may be a key factor in decreased amplitude of circadian rhythms [2]. Thus, older adults in particular may benefit from effectively timed bright light to strengthen the entrainment of the SCN to the solar light-dark cycle.

BLT is therefore an increasingly popular chronotherapy strategy [2]. Although the efficacy of BLT as an intervention strategy is currently inconclusive [303, 431], preliminary evidence for the use of BLT to promote sleep among older adults does appear promising. Two separate quasi-experimental interventions found that the subjective sleep quality of older women improved after six days of 1-hour morning BLT, although there were no changes in objective sleep quality.
Figure 1.16 Brief introduction to the neurophysiological response to light (Panel A) and its use in bright light therapy according to the phase response curve of light (Panel B)

Panel A: Darkness upregulates melatonin production—a hormone which helps regulate the sleep-wake cycle by increasing sleep signals. Light downregulates melatonin production, thus decreasing sleep signaling.

Panel B: Laboratory experiments indicate that when individuals are exposed to bright light in the evening or early morning prior to their core-body temperature minimum (~6 AM; CB_Tmin), it causes a phase delay (i.e., desire for sleep decreases and wakefulness increases). Individuals exposed to bright light in the morning after their CB_Tmin causes a phase advancement (i.e., desire for sleep increases and wakefulness decreases).
Twice-daily 1-hour BLT also improves subjective sleep quality in adults with Parkinson’s disease [434]. Another study determined that 8 hours of daily BLT improved objectively-measured sleep duration and cognitive function among nursing home residents [435]. Mishima and colleagues found that 2-hours of daily morning BLT significantly improved caregiver reported daily sleep duration and nocturnal sleep duration among older adults living with dementia [436].

While these results suggest that BLT might be a useful strategy for improving the sleep of older adults, the precise prescription of BLT to promote sleep is relatively unclear. At the present time, current evidence-based guidelines for the use of BLT to promote sleep and circadian regulation do not provide a clear and concise road-map for the prescription of BLT [437, 438]. Like PA and exercise training, it is largely unknown what frequency of BLT (e.g., morning vs. evening), intensity of light (10,000 lux vs. 100,000 lux), type of light (white light vs. blue light), or duration of BLT can best promote sleep. Even more importantly, the biological clock is not equally amenable to shifts at each phase in the circadian rhythm [291]. A zeitgeber can cause the biological clock to phase advance, phase delay, or be entirely phase neutral depending on the biological clock time at which a zeitgeber is administered. It is thus highly likely that successful BLT requires an individualized approach where proper timing, intensity, frequency, duration, and type of light is essential [2].

1.5.2.3.B Physical activity and exercise training

Another potential zeitgeber for use as chronotherapy is PA or PA in the form of exercise training [320, 384, 385]. Briefly, PA performed in the morning or early afternoon does not appear to have
a consistent effect on phase shifts of the biological clock; however, engaging in PA in the late afternoon causes a phase advance of the biological clock, while late night PA causes phase delay of the biological clock [384, 385]. The time-based response to how PA can impact the SCN is hypothesized to coincide with the timing of the opening of the sleep gate—the shift of the biological clock from generating a waking signal which reduces sleep need, to generating a signal which facilitates sleep [12].

However, the use of PA as a strategy to maintain circadian alignment may be challenging from a practical standpoint. The current evidence describing the effects of PA as a zeitgeber comes from controlled laboratory experiments, where the timing and intensity of PA in the form of exercise is tightly controlled. Conducting an intervention where participants would be asked to engage in regularly timed PA at a prescribed intensity would: 1) be burdensome to participants; and 2) require enormous resources to ensure participant adherence.

The current body of evidence therefore suggests that PA has chronobiotic effects, which may play a role in promoting good quality sleep. However, it is still unclear whether PA can improve the sleep of older adults given that circadian regulation – as well as the relationship between PA and sleep – appear to weaken with age.

1.5.3 Summary of current strategies to promote physical activity, reduce sedentary behaviour, and improve sleep and circadian rhythms

There are a number of different evidence-based methods for promoting PA and reducing SB. While there is no single best method for increasing PA and reducing SB, BAP offers an effective
evidence-based approach to PA and SB behaviour change which may be enhanced through wearable-technology. There is also no single best method for promoting sleep. Several promising evidence-based behavioural methods for promoting sleep include 1) CBT; 2) PA and exercise training; and 3) chronotherapy. One component of CBT that might also be beneficial for improving sleep is sleep hygiene education; however, sleep hygiene education should be combined with other therapies. PA and exercise training might also improve sleep, although the precise dose of PA or exercise training needed to promote sleep is still unclear. Chronotherapy is an evidence-based approach for improving sleep which uses effectively timed zeitgebers (i.e., BLT and PA or exercise training) in order to re-align the biological clock with the solar light-dark cycle. However, the precise timing and doses of each chronotherapeutic in order to improve sleep and circadian regulation are not known.

1.6 Summary of the current research gaps

The effects of PA, SB, and sleep on cognitive health are emerging; yet, much is still unknown about how these behaviours impact older adult cognitive health. Below are some of the major research gaps I have identified.

1.6.1 The impact of physical activity on cognitive health

While current evidence indicates that PA is associated with better cognitive health, the precise prescription of PA for cognitive health has been elusive. The current PA guidelines suggest that all older adults should obtain at least 150 minutes/week of MVPA for overall health, as well as cognitive health [439]. However, it is unclear whether this prescription needs to be modified for
individuals with a higher risk for dementia. Moreover, it is unclear whether certain types of PA are more beneficial for cognitive health.

1.6.2 The impact of sedentary behaviour on cognitive health

Far less is known about how SB impacts older adult cognitive health, and thus the question about how SB impacts cognitive health are preliminary. Most importantly, it is unclear if greater amounts of SB are associated with poorer cognitive function. It is also unknown what specific areas of cognition are affected by increased amounts of SB, and very little is known about how SB is associated with brain structure, function, or neurophysiological biomarkers. Finally, it is unclear if reductions in sedentary time can lead to improvements in cognitive health.

1.6.3 The impact of sleep and circadian rhythms on cognitive health

While it is clear that there is a bi-directional relationship between sleep and cognitive health, it is unclear whether improving sleep can improve cognitive health. In addition, objective and subjective measures of sleep do not correlate well and may measure different aspects of sleep [286]. Thus it still remains an open question whether improving subjective sleep quality, objective sleep quality, and/or sleep architecture provides similar (or differential) benefits to cognitive health.

Far less is known about how circadian rhythms can impact cognitive health. Although sleep quality is closely tied to circadian function, it is unclear whether improving circadian regulation can promote better sleep (or vice-versa). Importantly, there have been few attempts to use chronotherapy to promote older adult sleep [2]
1.6.4 The dynamic relationships of time-use activity behaviours with older adult cognitive health

There is an increasing amount of evidence that indicates PA, SB, and sleep are dynamically related to each other and older adult cognitive health; however, much is still unknown about these dynamic relationships and their implications on cognitive health. For example, it is unclear which time-use activity behaviour has the greatest impact on older adult cognitive health. It is also unclear whether PA, SB, and sleep impact cognitive health simultaneously, in synergy, or in silos. There is also little known about whether a combined therapeutic approach of 1) promoting PA; 2) reducing SB; 3) improving sleep quality; or 4) some combination of these strategies can improve the cognitive health of older adults.

The literature is also unclear if differences in PA and SB exist between older adults with MCI, and those without. Specifically, it is currently unknown whether differences in cognitive status can impact the relationships of PA and SB with cognitive health. Due to underlying neurobiological differences between older adults with MCI and those without [2], a functional weakening in the relationships of health behaviours with cognitive function may occur in MCI [147].

It is also unclear what the independent relationships of PA, SB, and sleep are with different aspects of cognitive health. For example, it is unknown whether PA has a stronger association with cognitive health than SB (or vice-versa). The same can also be said for the independent associations of PA (or SB) and sleep with cognitive health. Determining these relationships will
be a first step to grasping the independent contributions of these behaviours to older adult cognitive health.

While there is at least initial evidence that greater PA is linked with better sleep [11, 365], most of this evidence is based upon self-reported PA and self-reported sleep. Importantly, objective measures of PA and sleep often measure different things than subjective measures [122, 286]. While current evidence suggests the relationship between PA and sleep may be attenuated in older adults [365], few studies have examined why this might be. One potential reason for this apparent functional weakening in the relationship is that we simply need less sleep as we age [376]. It is also plausible that underlying changes in older adult neurobiology (e.g., neural atrophy, nocturnal hypoxia, neuroendocrine changes, and altered neuromodulation) may reduce the potential to impact sleep quality through strategies such as PA [296]. However, both of these hypotheses lack data from long-term observational studies, and it remains to be seen whether PA can modulate age-associated changes in sleep quality.

1.6.5 Strategies to promote physical activity, reduce sedentary behaviour, and improve sleep

A number of different strategies exist for promoting PA [440-443], reducing SB [397, 444], and improving sleep [398, 399]. Most strategies to increase PA and reduce SB have been only modestly effective, with improvements often being short-lived [445-447]. More research is needed about the long-term effectiveness of non-pharmacological sleep interventions [398]. There is also no evidence to date about the long-term effectiveness of PA and exercise training on sleep [428]. Importantly, it is largely unknown whether any of these strategies are effective methods of
behaviour change among older adults with cognitive issues (e.g., MCI), and whether these strategies can consequently improve cognitive health (either with or without cognitive impairment).

While there is preliminary evidence which supports chronotherapy as a technique for promoting sleep [2], the effectiveness of chronotherapy as a strategy to improve sleep and circadian rhythms is largely uncertain. Science has yet to determine the precise timing and prescription of BLT for promoting older adult sleep and circadian regulation, and the long-term efficacy of chronotherapy for improving sleep is hazy [448]. PA as chronotherapy is also still in its infancy [449]. While some preliminary evidence suggests that multimodal chronotherapy (i.e., BLT and PA) in conjunction with sleep hygiene might benefit sleep and cognitive health among older adults with MCI and dementia [448], larger sample sizes and more rigorous studies are needed in order to confirm these results.

1.7 Thesis overview

1.7.1 Main thesis questions

The previous sections provided quality evidence that PA, SB, and sleep are each important for older adult cognitive health. My thesis aims to extend our current knowledge in these areas by characterizing how each of these time-use activity behaviours are dynamically related to each other and cognitive health, as well as elucidate how to most effectively promote these behaviours in order to improve older adult cognitive health. Specifically, my thesis aims to answer the following research questions:
1. How are time-use activity behaviours associated with older adult cognitive health?
2. What is the dynamic relationship between time-use activity behaviours and older adult cognitive health?
3. Can we promote cognitive health in older adults with and without cognitive impairment through targeted interventions on time-use activity behaviours?

1.7.2 Methodology

Herein I outline the primary outcome measures I used throughout my thesis. I have highlighted most of these measures throughout Chapter 1, however I now include a brief description of each measure. Greater details about each measure are included in the relevant studies (Chapters 2-7).

1.7.2.1 Physical activity measures

I measured PA using the MW8, SWA, and CHAMPS questionnaire. Each of these measures have evidence of validity and reliability for estimating older adult PA [136, 137, 141-143, 146, 147, 149].

1.7.2.2 Sedentary behaviour measures

I measured SB using the MW8 and SWA. Both of these measures have evidence of validity and reliability for estimating older adult SB [136, 140].

1.7.2.3 Sleep measures

I measured sleep using the MW8, PSQI, and CSD. The MW8 is a tri-axial accelerometer designed to observe acceleration ranging in magnitude from 0.01G to 8G, with a frequency of 3-11Hz. The
MW8 is the updated version of the Actiwatch7, an actigraph with evidence of validity against PSG [450, 451]. There is also initial evidence of validity against PSG for the MW8 [298]. All measurements using the MW8 used 60 second epochs [452].

The PSQI is a 19-item questionnaire that assesses subjective sleep using ratings for 7 different aspects of sleep (i.e., global sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleep medication; and daytime dysfunction). Participants answer the questionnaire retrospectively, as the questionnaire surveys sleep components spanning the previous month. The questionnaire has good evidence of validity and reliability [301, 453].

Although not technically an outcome measure of sleep in my thesis, participants in the studies from Chapters 3, 4, and 7 were also given the 9-item CSD and asked to complete it each morning upon waking [452]. The responses from the CSD were used to confirm sleep windows as determined by the time stamped event markers. In cases where the event marker and CSD entry disagreed for the start time of the sleep window, we used activity cessation and light sensor data from the MW8 to determine “lights out”. Similarly, when the event marker and CSD entry disagreed for the end of the sleep window, we used activity onset and “lights on” to determine the end of the sleep window. If responses from the CSD entry disagreed with the event markers entered by participants as the start of the day (i.e., finished trying to sleep and awake and out of bed), we used activity onset and light sensor data to determine the start of the day. Similarly, when the event marker and CSD entry disagreed for the end of day (i.e., time spent trying to sleep), we used activity cessation and light sensor data to determine the end of the day.
1.7.2.4 Cognitive function measures

I measured global cognitive function in Chapters 3, 4, and 7 using the ADAS-Cog Plus [454]. The ADAS-Cog Plus uses a multidimensional item response theory model which can flexibly utilize item scores from multiple cognitive assessment instruments to generate a global cognitive function score and standard error of measurement for that score. Scores are defined by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort [455], wherein the mean score for cognitively healthy older adults is about -1.0, the mean for MCI is about 0.0, and the mean for dementia cases is about 1.0. Thus, higher scores indicate poorer cognitive performance. In Chapters 3 and 4, the ADAS-Cog plus score was computed using: 1) the 13-item ADAS-Cog [456]; 2) Montreal Cognitive Assessment (MoCA) [457]; 3) Trail Making Test A and B [458]; 4) Digit Span Forward and Backward [459]; and 5) verbal fluency [458]. In Chapter 7, we also included the Digit Symbol Substitution Test [460] in our computation of ADAS-Cog Plus. Appendix C provides a complete description of these measures.

In Chapter 6, I measured cognitive function using the National Institutes of Health Toolbox Cognition Battery (NIHTB-CB) [461]. Briefly, the NIHTB-CB provides a brief, convenient set of computerized and standardized measures of cognitive function. I examined two specific cognitive subdomains: 1) episodic memory using the picture sequence memory task [462]; and 2) working memory using the list-sorting task [463]. Briefly, the picture sequence memory task assesses episodic memory by having participants remember a sequence of actions embedded within a story. Participants re-arrange several pictures on the computer to match the sequence of events in the story. The list-sorting task assesses working memory by asking participants to repeat the names of orally—and visually—presented stimuli in order of size, from smallest largest. The number of
items per set increases from one trial to the next and is discontinued once 2 trials of the same length are failed.

1.7.2.5 Brain structure measures
I measured brain structure, specifically cortical thickness, using structural MRI. Structural MRI is a neuroimaging technique that permits quantification of brain volume, curvature, and surface area. This is typically accomplished using a semi-automated analysis pipeline on data acquired from a high-resolution T1-weighted image.

1.7.3 Overview of thesis chapters
To address the research questions, this thesis is comprised of six studies; each presented as a separate chapter. Figure 1.17 describes each of the observational studies included in my thesis (Chapters 2-5). Figure 1.18 describes the experimental studies included in my thesis (Chapters 6 and 7).

In Chapter 2, I investigated the current evidence examining the relationship of SB with older adult cognitive function. In this systematic review of observational studies examining the association of SB with older adult cognitive function, I determined that the current evidence suggests greater amounts of SB are associated with poorer cognitive function in later life. However, I also determined that the attributable risk of SB to dementia incidence is unclear at this time, and most of the current evidence for a relationship between SB and cognitive function was based on subjectively-measured SB.
Figure 1.17 Overview of the observational studies (Chapters 2-5) in the dissertation
In Chapter 3, I examined whether there are differences in the associations of objectively-measured PA and objectively-measured SB with cognitive function based on MCI status. I also examined whether there were differences in PA and SB levels between healthy older adults and older adults with MCI. In this cross-sectional study, I determined that older adults with MCI are less active and more sedentary than their healthy cognitive counterparts. In addition, I determined that the relationship of PA and SB with cognitive function is dependent on MCI status, such that there is a relationship between these behaviours and cognitive function for healthy older adults but not for older adults with MCI.
In Chapter 4, I assessed the independent relationships of objectively-measured PA and 1) objectively-measured sleep; and 2) subjectively-measured sleep with older adult cognitive function. In addition, I investigated the relationships of objectively-measured PA with objective and subjective sleep. In this cross-sectional study, I found that objectively-measured PA was associated with cognitive function independent of any measure of sleep. I also determined that objectively-measured sleep efficiency was associated with cognitive function independent of PA, however no other measure of sleep was associated with cognitive function. I did not find that PA was associated with any measure of sleep.

In Chapter 5, I assessed the independent relationships of objectively-measured PA and objectively-measured SB with brain cortical thickness. In this cross-sectional study, I found that PA was associated with greater cerebral cortical thickness in the left superior frontal gyrus and temporal pole, independent of SB. I did not find that SB was associated with brain cortical thickness independent of PA.

In Chapter 6, I examined whether an intervention to increase PA and reduce SB could also improve the cognitive function of older adults with knee osteoarthritis. I also examined whether increases in PA or reductions in SB were associated with improvements in cognitive performance. Using secondary cognitive outcomes from a proof-of-concept RCT, I determined that while the intervention significantly increased objectively-measured PA [145], there were no significant improvements in cognitive function. I also did not find that there was any association between changes in PA or SB and changes in cognitive function.
In Chapter 7, I investigated whether a multimodal chronotherapy intervention consisting of 1) individually-timed BLT; and 2) health coaching to promote PA in conjunction with general sleep hygiene education could improve the sleep and cognitive function of older adults with MCI. In this proof-of-concept RCT, I determined that multimodal chronotherapy significantly improved the subjective sleep quality of older adults with MCI, but did not significantly impact objectively-measured sleep. Furthermore, there were no significant improvements in cognitive function from the intervention, and improvements in sleep were not associated with improvements in cognitive performance.

This dissertation concludes by revisiting the proposed research questions with an integrated discussion on the dynamic relationships of PA, SB and sleep with older adult cognitive health. I will then provide an overview of the limitations of my thesis studies and also provide future directions.
Chapter 2: What is the association of sedentary behaviour and cognitive function? A systematic review


2.1 Introduction

Currently, one new case of all-cause dementia is detected every 4 seconds around the world [1]. All-cause dementia prevalence is also expected to rise since the number one risk factor is age [464], and the number of older adults worldwide is increasing [465]. Thus, the current lack of effective pharmaceutical treatments for all-cause dementia is creating an urgency to develop non-pharmacological strategies to prevent, or at least delay, the onset and progression of the disease [2]. As a result, lifestyle approaches have become an important line of scientific inquiry and public interest.

Increasing PA is one promising strategy to promote or maintain cognitive health in later life [197]. Accumulating empirical evidence suggests regular PA of an intensity ≥3.0 METs reduces the risk of all-cause dementia by 28% [156]. Thus, meeting current PA guidelines for older adults of 150 minutes/week of MVPA (i.e., activity of ≥3.0 METs) may help reduce all-cause dementia risk, prevent other comorbidities including type 2 diabetes and cardiovascular disease, and reduce all-cause mortality [95, 466, 467]. Since most older adults are physically inactive (i.e., do not engage in ≥150 minutes/week of MVPA) and fall short of these recommendations [96], increasing MVPA among older adults has become a public health priority. As such, it is estimated 17.7% of AD cases could be prevented by recommended amounts of MVPA [468].
Accumulating evidence also suggests high amounts of SB can increase morbidity and mortality risk [469]. SB is defined as any behaviour that incurs ≤1.5 METs and includes behaviours such as sitting, television watching, and lying down [8]. SB is associated with numerous health risks including type 2 diabetes [469], cardiovascular disease [266], and all-cause mortality [267]. Given the risks of SB to health, recommendations for sedentary time suggest limiting discretionary sedentary time to <2 hours/day and accumulating >2 hours/day of LPA (i.e., standing and light walking; [470, 471]). Emerging evidence also suggests SB is associated with cognitive function; however SB is a distinct behaviour from PA and thus a systematic review of the current epidemiological evidence is needed [6, 7].

While preliminary evidence suggests SB is associated with cognitive function, it is still unclear what the magnitude of this association is. For example, it is unclear if reducing SB is more important for long term cognitive health than increasing PA. Such empirical evidence is crucial to increasing our understanding of how we can best promote healthy cognitive aging through lifestyle approaches and determining whether public health should focus on reducing SB, increasing PA, or both to reduce all-cause dementia prevalence. Thus, our objective was to systematically review the epidemiological evidence regarding how SB is associated with cognitive function throughout the adult lifespan.

2.2 Methods

2.2.1 Summary of search strategy
We conducted a systematic review regarding the association between SB and cognitive function. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [472], we searched PubMed, PsychINFO, EBSCO, and Web of Science between January 1, 1990-February 6, 2016. Included in our search terms were the following keywords: SB terms (SB, physical inactivity, television time, TV time, screen time); cognition terms (cognition, cognitive function, brain function, executive function, memory, dementia, AD); and age terms (older adults, elders, elderly, aging, aged, 40+ years). This process was repeated until all search term combinations were performed.

2.2.2 Study selection

We selected peer reviewed, published, observational studies that included adults aged 40 years and older that measured SB as an exposure and cognitive function as an outcome. Articles mentioning SB and cognition in either the title or abstract were initially included for full-text review.

2.2.3 Inclusion and exclusion criteria

We included studies if they were: 1) observational studies (i.e., cohort, case-control, or cross-sectional); 2) peer-reviewed; and 3) published in the English language between January 1, 1990-February 6, 2016. All studies included clearly described participants as adults aged 40 years and older at baseline assessment and measured SB at baseline assessment or over time with the purpose of assessing risk (i.e., exposure). Additionally, the studies included measured cognitive function at baseline assessment or over time with the purpose of determining change associated with increased SB (i.e., outcome).
We excluded articles if they were: 1) not peer reviewed articles; and 2) not published in the English language. Since we were only interested in observational studies, interventions designed to reduce SB were not included.

2.2.4 Data extraction

Two authors (RSF and JCD) initially screened and identified studies based on the study title and abstract. Duplicates and articles failing to meet inclusion criteria were removed. The remaining full-text articles were reviewed by RSF and JCD to determine eligibility. Any disagreements were resolved by a third reviewer (TLA).

Two raters (RSF and JCD) independently extracted data from all articles included; discrepancies were discussed and reviewed by a third party (TLA). Data were extracted from the included articles using a custom data extraction form developed by RSF and JCD. We extracted the following categories: 1) study design; 2) participant characteristics, setting and length of follow-up; 3) measure of exposure (i.e., SB); 4) measure of outcome (i.e., cognitive function); and 5) main findings.

For exposure measures (i.e., SB), we extracted the: 1) instrument name; 2) exposure definition (e.g., SB or television time); 3) method of exposure assessment (e.g., self-report questionnaire, accelerometry, etc.); 4) data collection procedure; 5) statistical methodology; and 6) previously established validity and reliability of the instrument. For exposure definitions, SB included time spent engaging in activities with an energy cost of ≤1.5 METs and television time referred to sedentary time spent watching television.
For methods of assessment of cognitive function, we extracted the: 1) instrument name; 2) domain of cognitive function assessed; 3) method for assessing cognitive function; 4) statistical methodology; and 5) previously established validity and reliability for the instrument. Given the limited number of studies available and the heterogeneity of samples used in these studies, we did not perform a meta-analysis.

2.2.5 Assessment of study quality

Two authors (RSF and JCD) assessed the quality of the articles via the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [473]. The STROBE checklist contains 22 separate items to identify the quality of reporting for observational studies. In summary, we assessed study quality based on the following components: 1) an informative and balanced abstract; 2) clear scientific background, rationale, objectives, and hypothesis; 3) clear description of study design, methodology, outcomes and exposures, and statistical analyses; 4) clear description of potential biases and how these were limited; 5) clear description of study participants, incidence of loss to follow-up, and reporting of both outcomes and exposures; 6) clear reporting of all results and analyses; 7) clear summarization of study findings with reference to study objectives; 8) clear description of the limitations of the study; and 9) a cautious overall interpretation of the findings with reference to the generalizability of the findings.

Two raters (RSF and JCD) independently rated the quality of the studies and achieved consensus through discussion (K=0.90). Discrepancies were settled by a third author (TLA). We used a binary system (+ =Yes, - =No) for each item of interest on the STROBE checklist. High quality studies
were defined as studies missing fewer than three criteria of the STROBE checklist, while low quality studies were defined as studies missing three or more criteria.

2.3 Results

2.3.1 Search results and study characteristics

Figure 2.1A provides a sample of the search strategy and 2.1B describes the results of the search strategy for articles examining the association of SB with cognitive function. Of the 485 articles initially identified by title and abstract screening, our final systematic review included eight articles [474-481].

Study characteristics are described in Table 2.1. Three studies used a cohort design [474-476], one was a nested case-control [477], one used a case-control design [478], and three studies used a cross-sectional design [479-481]. The average follow-up time from the cohort studies was 7.67 years [474-476], and the follow-up time for the nested case-control study was 21 years [477]. Sample sizes ranged from 125-6359 participants with samples from England, Finland, France, and the United States.
Figure 2.1 Study selection process and sample search strategy

**Term 1:** Sedentary Behavior, Television Time, TV Time, Screen Time

**Term 2:** Cognition, Cognitive Function, Brain Function, Executive Function, Memory, Dementia, Alzheimer's disease

**Term 3:** Older Adults, Elderly, Elders, Aged, Aging, 40+ years

Limited to: 1990-Current

**Sample Strategy:**

1. Sedentary behavior and Cognition and Older Adults
2. Sedentary behavior and Cognition and Elders
3. Sedentary behavior and Cognition and Elderly
4. Sedentary behavior and Cognition and Aging
5. Sedentary behavior and Cognition and Aged
6. Sedentary behavior and Cognition and 40+ years
7. Sedentary behavior and Cognitive Function and Older Adults
8. Sedentary behavior and Cognitive Function and Elders
9. Sedentary behavior and Cognitive Function and Elderly
10. Sedentary behavior and Cognitive Function and Aging
11. Sedentary behavior and Cognitive Function and Aged
12. Sedentary behavior and Cognitive Function and 40+ years
<table>
<thead>
<tr>
<th>Publication &amp; Study Design</th>
<th>Participants, Country, Setting, &amp; Length of Follow-Up</th>
<th>Sedentary Behaviour (exposure assessment)</th>
<th>Cognitive Function (outcome assessment)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamer &amp; Stamatakis [474]</td>
<td>2014 Cohort design 6359 men and women from the English Longitudinal Study of Ageing England 2 year follow-up</td>
<td>Self-reported TV viewing considered sedentary behaviour (SB).</td>
<td>Immediate word recall, delayed word recall, and verbal fluency [482]. All three used to create a global cognitive function score (primary outcome).</td>
<td>Linear inverse relationship between TV time and cognitive function. Decreased cognition from baseline (EMM= 0.39, 95% CI: [0.33, 0.45]) to follow-up (EMM= 0.25, 95% CI: [0.19, 0.31]), but no association between baseline SB and changes in cognitive function.</td>
</tr>
<tr>
<td>Kesse-Guyot et al. [475]</td>
<td>2014 Cohort design 2430 participants from the Supplémentation en Vitamines et Minéraux Antioxydants study France 13 year follow-up</td>
<td>Self-administered French version of the Modifiable Activity Questionnaire (MAQ) [483]. Participants reported average time spent at home watching TV (min/day).</td>
<td>Digit Span forward and backward (primary outcome) [459], Delis-Kaplan trail making test [484], RI-48 cued recall test [485], Semantic fluency and phonemic fluency [486].</td>
<td>SB associated with decreased global cognitive function (β= -1.28; 95% CI: [-2.46, -0.11]) and decreased verbal memory (β= -1.38; 95% CI: [-2.58, -0.18]) over time.</td>
</tr>
<tr>
<td>Kesse-Guyot et al [476]</td>
<td>2012 Cohort design 2579 participants who agreed to participate in the follow-up period of the Supplémentation en Vitamines et Minéraux Antioxydants study France 8 year follow-up</td>
<td>Self-administered French Modifiable Activity Questionnaire (MAQ) [483]. Participants asked about average daily time spent with SB (min/day).</td>
<td>Phonemic and semantic fluency (primary outcome) [486], RI-48 test [485], digit span forward and backward [459], Delis-Kaplan trail-making test [484].</td>
<td>Negative association observed between TV viewing and executive function cross-sectionally (β=-0.98; 95% CI: [-1.93, -0.04]), no association between executive function and SB over time.</td>
</tr>
</tbody>
</table>
Table 2.1 Continued

<table>
<thead>
<tr>
<th>Publication &amp; Study Design</th>
<th>Participants, Country, Setting, &amp; Length of Follow-Up</th>
<th>Sedentary Behaviour (exposure assessment)</th>
<th>Cognitive Function (outcome assessment)</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Case-control designs</strong></td>
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<tr>
<td>Kivipelto et al. [477]</td>
<td>1449 participants from the Cardiovascular Risk Factors, Aging and Dementia study (65-79 years)</td>
<td>Self-reported leisure time physical activity (PA) dichotomized into categories: active and sedentary (persons who participated in leisure time PA less than two times per week).</td>
<td>Cognitive status determined via scores on the MMSE [487], and all-cause dementia diagnosis (primary outcome) confirmed according to the Diagnostic and Statistical Manual of Mental Disorders [488].</td>
<td>The odds of developing all-cause dementia were 2.07 times greater for participants who were sedentary (95% CI: [1.12-3.86]) as compared to physically active when controlling for age, sex, follow-up time, education, BMI, cholesterol, blood pressure, heart attack, stroke and diabetes.</td>
</tr>
<tr>
<td>Lindstrom et al. [478]</td>
<td>Participants born between 1915 and 1944. 135 cases of Alzheimer’s disease 331 controls recruited from clinical settings and from the community.</td>
<td>Participants self-reported daily hours of television viewing.</td>
<td>Diagnosed case of Alzheimer’s disease (primary outcome).</td>
<td>Cases watched significantly more television than controls (F [1, 464]= 35.37). The odds of developing Alzheimer’s disease increased 1.32 times for every hour of daily television viewing (95% CI: [1.08-1.62]).</td>
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<td><strong>Cross-sectional designs</strong></td>
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<tr>
<td>Rosenberg et al. [479]</td>
<td>307 older adults (67-100 years) from 11 retirement communities</td>
<td>Self-reported sedentary behaviour assessed using a modified version of the Sedentary Behaviour Questionnaire [489].</td>
<td>Trail Making Test [491]</td>
<td>Self-reported sedentary time was associated with improved performance on Trails A ($\beta=-0.01 \pm 0.01$), but was not associated with improved executive performance. Objectively-measured sedentary time was not associated with Trail Making Test performance.</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>Objective sedentary time measured using ActiGraph GT3X+ accelerometer [490].</td>
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<tr>
<td>Publication &amp; Study Design</td>
<td>Participants, Country, Setting, &amp; Length of Follow-Up</td>
<td>Sedentary Behaviour (exposure assessment)</td>
<td>Cognitive Function (outcome assessment)</td>
<td>Results</td>
</tr>
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<tr>
<td>Steinberg et al. [480]</td>
<td>125 healthy adults 65 or older with no clinical evidence of cognitive impairment</td>
<td>Hours spent in SB according to the Community Health Activity Program for Seniors (CHAMPS) questionnaire [149].</td>
<td>CogState computerized battery measured multiple domains of cognition including: psychomotor speed, visual attention, visual recognition, and memory (primary outcome) [492].</td>
<td>Lower scores on executive function measures associated with increased SB (β = 0.006 ± 0.003; R² = 0.2323). Memory scores and processing speed were not associated with increased SB.</td>
</tr>
<tr>
<td>Vance et al. [481]</td>
<td>158 participants with a mean age of 75.05 years were recruited from the Accelerate study</td>
<td>The total amount of time spent sitting, sleeping, or lying down was used as an indicator of SB [493].</td>
<td>Benton Visual Retention Test [494], Trail-Making Test [491], and the Rey-Osterrieth Complex Figure Copy and Recall Tests [495]. A composite score for cognitive function was then created (primary outcome).</td>
<td>Structural equation modeling predicted SB was associated with increased cognitive function (β = 0.34)</td>
</tr>
</tbody>
</table>
2.3.2 Measurement of sedentary behaviour

Measurement of SB varied considerably with a total of eight different measures used across the eight studies, as described in Table 2.2. All eight studies measured exposure to SB via subjective methods [474-481], and one study measured SB via an objective method (accelerometry) [479]. Five studies measured exposure as sedentary time (i.e., time spent sitting, lying down or sleeping) [476, 477, 479-481], and four studies measured exposure as TV time [474-476, 478]. One study measured the exposure as both TV time and sedentary time [476].

Five studies examined SB using a previously developed questionnaire [475, 476, 479-481]. Two studies [475, 476], used the Modifiable Activity Questionnaire (MAQ) to assess SB [483]. A single study [480], used the CHAMPS questionnaire [146, 147, 149, 150]. Another study [479], used the Sedentary Behaviour Questionnaire (SBQ; [489]). The last study [481], used an unnamed questionnaire developed from previous investigations to assess sedentary time [493]. Each of the four questionnaires showed evidence of validity and reliability, however only the MAQ, CHAMPS, and SBQ were previously validated against a criterion measure [146, 147, 149, 150, 489, 496].

A single study [479], used an accelerometer, the Actigraph GT3X+ [490], to measure SB objectively. Accelerometers show good evidence of validity [497, 498]; however there is no current minimum wear standards for reliable SB estimates.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Name of Measure(s)</th>
<th>Definition of Exposure</th>
<th>Type of Exposure Assessment</th>
<th>Data Collection Procedure</th>
<th>Statistical Methods and Confounder Adjustment</th>
<th>Validity and Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamer &amp; Stamatakis, 2014 [474]</td>
<td>Unknown</td>
<td>TV time</td>
<td>Subjective Measure</td>
<td>Participants self-reported daily television time and engagement in vigorous, moderate, and low-intensity PA.</td>
<td>Type of regression: Linear mixed models with random effect intercept; Covariates and confounders: age sex, smoking, alcohol, PA, social status, disability, chronic illness and body mass index (BMI).</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kesse-Guyot et al., 2014 [475]</td>
<td>Modifiable Activity Questionnaire (MAQ) [483]</td>
<td>TV time</td>
<td>Subjective Measure</td>
<td>Participants self-reported average daily time spent watching TV and leisure-time PA performed at least 10 times for at least 10 minutes per session over the past year including the frequency and duration. After multiplying the number of hours/week of each activity by the estimated metabolic equivalent (MET), a summary score was obtained.</td>
<td>Type of regression: structural equation modeling; Covariates and confounders: age, gender, education, time-lag between baseline and cognitive evaluation, occupation, energy intake, number of 24-hour records, BMI, depressive symptoms, memory issues, diabetes, hypertension, and cardiovascular disease</td>
<td>Validity: ( r = 0.65 ) [496] Reliability: ICC= 0.77 [496]</td>
</tr>
<tr>
<td>Publication</td>
<td>Name of Measure(s)</td>
<td>Definition of Exposure</td>
<td>Type of Exposure Assessment</td>
<td>Data Collection Procedure</td>
<td>Statistical Methods and Confounder Adjustment</td>
<td>Validity and Reliability</td>
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<tr>
<td>Kesse-Guyot et al., 2012 [476]</td>
<td>Modifiable Activity Questionnaire (MAQ) [483]</td>
<td>Sedentary behaviour (SB; TV time, computer use, reading)</td>
<td>Subjective Measure Questionnaire designed to assess SB and PA during past 12 months.</td>
<td>Participants self-reported average daily time spent watching TV, using a computer or reading (min/day)</td>
<td>Type of regression: Principal component analysis; Covariates and confounders: interval between SB assessment and cognitive evaluation, age, gender, education, occupation, retirement status, tobacco use, BMI, depressive symptoms, health status, heart disease, diabetes, hypertension and PA.</td>
<td>Validity: r= 0.65 [496] Reliability: ICC= 0.77 [496]</td>
</tr>
<tr>
<td>Kivipelto et al., 2008 [477]</td>
<td>Unknown</td>
<td>SB (leisure time PA &lt;2x/week)</td>
<td>Subjective Measure Questionnaire developed by authors</td>
<td>Participants self-reported leisure-time PA lasting &gt;30 minutes and caused breathlessness and sweating. Participants dichotomized into active (&gt;2x/week) and sedentary (&lt;2x/week).</td>
<td>Type of regression: Multiple logistic regressions; Covariates and confounders: age, sex, follow-up time, education, BMI, cholesterol, blood pressure, heart attack, stroke and diabetes mellitus.</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lindstrom et al., 2005 [478]</td>
<td>Unknown</td>
<td>Daily hours of television viewing</td>
<td>Subjective Measure Questionnaire developed by authors</td>
<td>Participants self-reported hours/month devoted to TV viewing at age 20-39 and at ages of 40-59. Daily TV viewing hours calculated from total hours/day spent watching TV.</td>
<td>Type of regression: Unconditional logistic regression model</td>
<td>Unknown</td>
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<tr>
<td>Publication</td>
<td>Name of Measure(s)</td>
<td>Definition of Exposure</td>
<td>Type of Exposure Assessment</td>
<td>Data Collection Procedure</td>
<td>Statistical Methods and Confounder Adjustment</td>
<td>Validity and Reliability</td>
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<tr>
<td>Rosenberg et al., 2015 [479]</td>
<td>Self-report measure: Sedentary Behavior Questionnaire (SBQ) [489]</td>
<td>SBQ: Subjective Measure</td>
<td>SBQ: Hours spent in SB</td>
<td>SBQ: Participants reported time/day spent in SB including sitting, watching TV, computer use, reading, commuting, napping, and other activities.</td>
<td>Type of regression: linear mixed-effects models</td>
<td>SBQ: Validity: No significant relationship between accelerometer counts and SBQ scores; Reliability: ICC= 0.85 [489]</td>
</tr>
<tr>
<td></td>
<td>Objective measure: Actigraph GT3X+: Objective Measure</td>
<td>Actigraph GT3X+: Hours spent in SB</td>
<td>Actigraph GT3X+: Participants were included with at least 1 valid day of wear time and 600 minutes of accelerometer data. Sedentary time was assessed using the standard cutpoint of &lt;100 counts per minute.</td>
<td>Covariates and confounders: age, gender, marital and educational status.</td>
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<tr>
<td>Steinberg et al., 2014 [480]</td>
<td>Community Health Activity Program for Seniors (CHAMPS) questionnaire [148]</td>
<td>Community Health Activity Program for Seniors (CHAMPS) questionnaire [148]</td>
<td>Community Health Activity Program for Seniors (CHAMPS) questionnaire [148]</td>
<td>Participants self-reported weekly frequency and duration of 40 different activities undertaken by older adults</td>
<td>Type of regression: linear regression analyses</td>
<td>Validity: r= 0.29 Test-retest reliability: ICC= 0.76. [146, 147, 149]</td>
</tr>
<tr>
<td>Publication</td>
<td>Name of Measure(s)</td>
<td>Definition of Exposure</td>
<td>Type of Exposure Assessment</td>
<td>Data Collection Procedure</td>
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<tr>
<td>Vance et al., 2005 [481]</td>
<td>Unknown</td>
<td>Total amount of time spent sitting, sleeping, or lying down used as an indicator of SB</td>
<td>Subjective Measure Questionnaire adapted from Paffenbarger questionnaire [493]</td>
<td>Participants self-reported how many hours per day spent seated, lying down, and sleeping.</td>
<td>Types of regression: Latent growth model; Covariates and confounders: Age, depression, and PA.</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
2.3.3 Measurement of outcomes from sedentary behaviour

Table 2.3 describes the measures of cognitive function used. Thirteen different measures of cognitive function were used across the eight studies [474-481]. Studies examined the following areas of cognition: 1) five measured memory [474, 475, 480, 481]; 2) five measured executive function [474-476, 479, 481]; 3) four measured processing speed [474, 479-481]; 4) two measured incidence of cognitive impairment or all-cause dementia [477, 478]; and 5) one measured perceptual organization and planning [481]. Three studies created scores for global cognitive function [474, 480, 481].

2.3.3.1 Assessment of memory

The constructs of memory measured were non-descriptive memory (i.e., unspecified by the authors as to what construct of memory the test measured), lexical-semantic memory, working memory, visual memory and episodic memory. Non-descriptive memory was measured via delayed word recall [482] in one study [474], and the Benton Visual Retention Test [494] in another study [481]. Lexical-semantic memory was measured via phonemic and semantic fluency [486] in two studies [475, 476]. Working memory was measured by digit span forward and backward [459] in two studies [475, 476]. Visual memory was assessed using the Rey-Osterriety Complex Figure Copy and Recall Test [495] in one study [481]. Episodic memory was measured via the RI-48 test [485] in two studies [475, 476]. Among the measures used, the Benton Visual Retention Test, phonemic and semantic fluency, digit span forward and backward, Rey-Osterriety Complex Figure Copy and Recall Test and the RI-48 have evidence of validity and reliability [485, 495, 499, 500].
<table>
<thead>
<tr>
<th>Publication</th>
<th>Domain of Cognitive Function Assessed (Name of Measure)</th>
<th>Data Collection Procedure</th>
<th>Analyses Utilized</th>
<th>Validity and Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort designs</strong></td>
<td></td>
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<tr>
<td>Hamer &amp; Stamatakis, 2014 [474]</td>
<td>Processing speed (Immediate word recall), Memory (Delayed word recall), and Executive function (Verbal fluency) [482].</td>
<td>Immediate word recall: Read 10 words and recalled as many words as possible immediately after. Delayed word recall: Using same list, recalled words after they completed other cognitive function tests. Verbal fluency: Named as many animals as possible in one minute. A global cognitive function score calculated from the sum of standardized scores on each test.</td>
<td>Type of regression: Linear mixed models with random effect intercept; Covariates and confounders: age, sex, smoking, alcohol, physical activity, social status, disability, chronic illness and body mass index (BMI).</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kesse-Guyot et al., 2014 [475]</td>
<td>Lexical-semantic memory (Phonemic fluency and semantic fluency [486]), Episodic memory (RI-48 test [485]), Working memory (Digit span forward and backward [486]), Executive function (Delis-Kaplan trail-making test [484]).</td>
<td>Phonemic fluency: Cited as many words as possible in 2 minutes beginning with the letter “p”. Semantic fluency: Named as many animals as possible in 2 minutes. RI-48 test: Delayed cued recall test. Digit span forward and backward: Repeated sequence of 7 digits, forward and backward. Trail making test: connecting numbers and letters alternating between the two series.</td>
<td>Type of regression: structural equation modeling; Covariates and confounders: age, gender, education, time-lag between baseline and cognitive evaluation, occupation, energy intake, number of 24-hour records, BMI, depressive symptoms, memory issues, diabetes, hypertension, and cardiovascular disease.</td>
<td>Phonemic and semantic fluency: Test re-test reliability r= 0.82 [499]. RI-48: Classified 88% of people with mild cognitive impairment (MCI) or Alzheimer’s Disease (AD) correctly [485]. Digit Span: B= 0.64 in Confirmatory Factor Analysis [500]. Trail Making: r= -0.38 compared to Stroop Color Word score [501].</td>
</tr>
<tr>
<td>Publication</td>
<td>Domain of Cognitive Function Assessed</td>
<td>Data Collection Procedure</td>
<td>Analyses Utilized</td>
<td>Validity and Reliability</td>
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<tr>
<td>Kesse-Guyot et al., 2012 [476]</td>
<td>Lexical-semantic memory (Phonemic fluency and semantic fluency [486]), Episodic memory (RI-48 test [485]), Working memory (Digit span forward and backward [486]), Executive function (Delis-Kaplan trail-making test [484]).</td>
<td>Phonemic fluency: Cited as many words as possible in 2 minutes beginning with “p”. Semantic fluency: Named as many animals as possible in 2 minutes. RI-48 test: Delayed cued recall test. Digit span forward and backward: Repeated sequence of 7 digits, forward and backward. Trail making test: connecting numbers and letters alternating between the two series.</td>
<td>Type of regression: Principal component analysis;</td>
<td>Phonemic and semantic fluency: Test re-test reliability r= 0.82 [499]. RI-48: Classified 88% of people with mild cognitive impairment (MCI) or Alzheimer’s Disease (AD) correctly [485]. Digit Span: B= 0.64 in Confirmatory Factor Analysis [500]. Trail Making: r= -0.38 compared to Stroop Color Word score [501]</td>
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### Case-control designs

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<tr>
<th>Publication</th>
<th>Domain of Cognitive Function Assessed</th>
<th>Data Collection Procedure</th>
<th>Analyses Utilized</th>
<th>Validity and Reliability</th>
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<tr>
<td>Kivipelto et al., 2008 [477]</td>
<td>Screened for cognitive impairment and all-cause dementia.</td>
<td>Mini-Mental State Exam (MMSE; [487]) at screening phase and for those who scored &lt;24, neuropsychological examinations conducted to screen for all-cause dementia, according to the Diagnostic and Statistical Manual of Mental Disorders [488].</td>
<td>Type of regression: Multiple logistic regressions;</td>
<td>MMSE: Test re-test reliability: r= 0.89; Validity: r= 0.78 compared to Verbal IQ &amp; r= 0.66 compared to Performance IQ [487].</td>
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<tr>
<td>Lindstrom et al., 2005 [478]</td>
<td>Screened for AD.</td>
<td>Cases evaluated by neuropsychological, laboratory and neurological examinations.</td>
<td>Type of regression: Unconditional logistic regression model</td>
<td>Unknown</td>
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<tr>
<td>Publication</td>
<td>Domain of Cognitive Function Assessed (Name of Measure)</td>
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<td>Rosenberg et al., 2015 [479]</td>
<td>Executive function and Processing speed (Trail Making Test [491])</td>
<td>Trails A was completed first, followed by Trails B. Both items were scored using completion time in seconds and scores for participants who were unable to complete the exam were set to the maximum value (300 seconds). Executive function was estimated by subtracting time of Trails A from Trails B.</td>
<td>Type of regression: linear mixed-effects models</td>
<td>Trail-Making Test: Reliability r= 0.60-0.90 [491]; Discriminat Validity: t= 16.20 (p&lt;0.001) [501].</td>
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<td>Steinberg et al., 2014 [480]</td>
<td>CogState computerized battery[492]. Cognitive tests assessed: 1) Processing speed; 2) Visual attention, recognition, and memory; 4) Verbal learning and memory; 5) Immediate recall; 6) Delayed recall; 7) Working memory; and 8) Problem solving and reasoning.</td>
<td>Participants administered the CogState tests over a 35-minute period.</td>
<td>Type of regression: linear regression analyses</td>
<td>Validity: r= 0.49-0.83 [502]</td>
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<tr>
<td>Vance et al., 2005 [481]</td>
<td>Memory (Benton Visual Retention Test [494]); Processing speed and Executive function (Trail Making Test [501]); Visual memory, perceptual organization and planning (Rey-Osterriety Complex Figure Copy and Recall Tests [491]).</td>
<td>Benton Visual Retention Test: Shown a series of geometric designs and then draw from memory. Trail-Making Test: Connected 25 alternating number and letter circles in sequence as quickly as possible. Rey-Osterriety Complex Figure and Recall Tests: Reproduced complex figure while present and then from memory.</td>
<td>Types of regression: Latent growth model;</td>
<td>Benton Visual Retention Test: Interrater reliability r= 0.80-0.90 [494].</td>
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2.3.3.2 Assessment of executive function

Two studies used the Delis-Kaplan Trail Making Test [484] to assess executive function [475, 476]. One study [474], used verbal fluency [482], and two studies [479, 481] used Trail Making Test [491]. The Delis-Kaplan Trail Making Test and the Trail Making Test both have evidence of validity and reliability [458, 491, 501].

2.3.3.3 Assessment of processing speed

Processing speed was measured via Immediate Word Recall [482] in one study [474], and by Trail Making Test [491] in two studies [479, 481]. Only Trail Making Test has evidence of validity and reliability [458, 491, 501].

2.3.3.4 Assessment of cognitive impairment and all-cause dementia incidence

One study [477] used the Mini-Mental State Exam (MMSE; [487]) to screen for cognitive impairment and then conducted neuropsychological exams to screen for all-cause dementia according to the Diagnostic and Statistical Manual of Mental Disorders [488]. The other case-control study [478], screened for cases of AD using unstated neuropsychological, laboratory and neurological examinations. Evidence of validity and reliability exists for the MMSE [487].

2.3.3.5 Assessment of perceptual organization and planning

The study measuring perceptual organization and planning [481], used the Rey-Osterriety Complex Figure Copy and Recall Test [495]. Evidence of validity and reliability exists for the Rey-Osterriety Complex Figure and Recall Test [495].
2.3.3.6 Assessment of global cognitive function

One study [480], used the CogState computerized battery to assess global cognitive function [492]. Another study [474], created a standardized global cognitive function score from the three cognitive measures used in the study: Immediate Word Recall, Delayed Word Recall, and Verbal Fluency [482]. The final study to measure global cognitive function [481], used a standardized score from the Benton Visual Retention Test [494], Trail Making Test [491], and Rey-Osterriety Complex Figure Copy and Recall Test [495]. Only the CogState computerized battery has evidence of validity and reliability as a global cognition measure [502].

2.3.4 Quality assessment

Studies varied considerably in quality as shown in Table 2.4. On average, studies met 19 of the 22 specific criteria of the STROBE checklist [474-481]. One article met all guidelines for the reporting of information [475], however three studies failed to address four or more different criteria of the STROBE checklist [478-480]. All four of the high quality studies found negative associations between SB and cognitive function [474-477].

The common issues were in failure to report: 1) study size (N= 4; [478-481]); 2) information about the design in the title and abstract (N= 4; [477, 479-481]); 3) potential biases (N= 4; [478-481]); and 4) specific objectives and hypotheses (N= 3; [474, 477, 480]). Other issues in study quality included failure to report: 1) eligibility criteria (N= 1; [478]); 2) sources of data and method of assessment (N= 1; [478]); 3) describing statistical analyses (N= 1; [476]); 4) providing a cautious overall interpretation of the study (N= 1; [479]); 5) discussing the generalizability of the findings (N= 1; [479]); and 6) outcomes, exposures and potential confounders (N= 1; [479]).
Table 2.4 Quality assessment for studies on the relationship of sedentary behaviour with cognitive function

<table>
<thead>
<tr>
<th>STROBE Checklist</th>
<th>Cohort designs</th>
<th>Case-control designs</th>
<th>Cross-sectional designs</th>
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1The STROBE Checklist asks the following information (+=Reported; - = Not reported):
1) Indicates study design in title and abstract and provides an informative and balance summary in the abstract
2) Gives the scientific background and rationale
3) States specific objectives and hypotheses
4) Presents key elements of study design
5) Describes setting, location, exposures, follow-up and relevant dates
6) Clearly defines eligibility criteria and methods of selecting participants
7) Clearly defines outcomes, exposures, potential confounders, predictors and effect modifiers
8) Gives sources of data and clearly defines method of assessment
9) Describes potential bias
10) Explains how study size was arrived at
11) Explains how quantitative variables were handled in analysis
12) Describes all statistical analyses
13) Reports number of individuals at each stage of study and gives reasons for non-participation
14) Gives characteristics of study participants and indicates number of missing data
15) Reports number of events (outcomes and/or exposures)
16) Clearly provides the main results of analyses
17) Reports all other analyses done
18) Summarizes key findings with reference to study objectives
19) Discusses limitations of the study
20) Provides a cautious overall interpretation of the study
21) Discusses the generalizability of the findings
22) Gives the sources of funding and role of the funders
2.3.5 Findings from studies on the association of sedentary behaviour with cognitive function

In total, six studies found associations between increased SB and decreases in cognitive function [474-479]. Two studies found associations between increased SB and improved cognitive function [479, 481].

2.3.5.1 Cohort designs

Among the cohort studies, one study found an association between increased SB and decreases in cognitive function over time [475]. The other two studies found associations between increased SB and lower cognitive function at baseline, but no association between SB and cognition over time [474, 476].

2.3.5.2 Case-control designs

The nested case-control study found the odds of developing all-cause dementia were higher for individuals who engaged in more SB [477]. In addition, the other case-control study found that individuals who watched more hours of television per day had higher odds of developing AD in later life [478].

2.3.5.3 Cross-sectional designs

The results of the cross-sectional studies were mixed. One study found associations between increased SB and lower cognitive function [480]. A second study found SB was positively associated with cognitive function [481]. The final cross-sectional study found subjectively-
measured SB was positively associated with processing speed; however there was no association between SB and cognitive function when measured objectively [479].

2.4 Discussion

2.4.1 Summary of main findings

Our results indicate SB is associated with reduced cognitive function over the lifespan. Importantly, all four of the high quality studies found SB is associated with poorer cognitive function. However, the heterogeneity in the current methods used to quantify SB and cognitive function are the current major barriers to determining the precise magnitude of this relationship. We also found only one study used an objective measure of SB and a number of exposure measures lacked evidence of validity and reliability.

Furthermore, two of the three longitudinal studies had follow-up periods of <10 years, which may account for the significant findings at baseline but not over time [474, 476]. Changes in cognition occur gradually over the adult lifespan [27], often with detectable changes occurring after the age of 60 [503]. As such, studies with short-term follow-ups (i.e., <10 years) may not detect meaningful associations between changes in cognition and lifestyle behaviours.

2.4.2 Comparison of the findings with the literature

A large body of work on the association between PA and better cognitive function exists [156], however far less is known about the association of SB with cognition. Some preliminary findings
have suggested that SB is associated with later life cognitive impairment, but have also noted a lack of epidemiological evidence needed to draw strong conclusions [6, 7].

Our review suggests SB is indeed associated with impaired cognitive function and all-cause dementia risk. Specifically, higher quality studies [474-477], and those of stronger epidemiological evidence (i.e., cohort or case-control design) all found associations between increased SB and poorer cognition [474-478]. Moreover, the current evidence suggests an association by meeting five of the nine epidemiological criteria for causation [155]. Specifically, the criteria met include: 1) consistent findings across persons, places, and circumstances; 2) evidence of temporality; 3) evidence of a dose-response relationship; 4) a plausible mechanism by which exposure leads to outcome; and 5) by analogy, the exposure is associated with outcome. Importantly, our systematic review found consistency in the findings [474-478, 480], evidence of temporality [475, 477, 478], and evidence of a dose-response relationship [474-476, 480].

In addition to our findings, a plausible mechanism by which SB is associated with cognitive decline is emerging. Recent data suggest prolonged sedentary time impairs glucose and lipid metabolism [88], which are both recognized as risk factors for cognitive decline and all-cause dementia [262, 263]. There is also evidence that SB is related to cognitive decline by analogy. Briefly, SB is associated with many chronic diseases [266, 267, 469, 504], which are also associated with cognitive impairment and dementia risk [268-270]. Thus, the evidence collectively suggests SB is a risk factor for later life cognitive impairment and all-cause dementia risk.

2.4.3 Assessment of sedentary behaviour
While our findings suggest there is now enough evidence to consider SB a risk factor for cognitive decline and dementia, the current measurement of SB still has some limitations. First, only one of the studies reviewed measured SB with an objective measure [479]. While there is no one best measure for assessing SB [505], and both objective measures and subjective measures have limitations [112], objective measures are considered to be more accurate and reliable because they eliminate recall bias [117]. This is because PA participation among older adults is often intermittent, sporadic or unstructured, which makes recall extremely difficult [506]; thus older adults may unintentionally over-report their SB [507]. However, this does not mean subjective methods of assessing SB are useless. Complete data from objective measures have an inherent selection bias which limits the generalisability of the findings, and objective assessment may miss components or dimensions of SB which may be health protective [117]. Thus, future research examining the association of SB with cognitive function should utilize both objective and subjective measures whenever possible [508].

Secondly, four of the eight studies we reviewed used measures of SB with no previous evidence of validity or reliability [474, 477, 478, 481]. Validity and reliability are important for making sound interpretations from tests and thus the lack of evidence of either calls into question the conclusions drawn from these studies [123, 125]. The continued use of measures without evidence of validity and reliability is making the conclusions drawn from these studies questionable at best, and downright wrong at worst [122].

Finally, the construct of SB was misclassified in several of the studies. For example, Kivipelto and colleagues categorized participants as sedentary based on self-reported leisure-time PA of less than
twice per week [477]. Yet the absence of PA does not define SB [265], and thus misclassification in the literature poses challenges to accurately assessing the association between SB and cognitive function.

2.4.4 Assessment of cognitive function

While the current measurement of cognitive function in the studies reviewed appears to be more rigorous than the methods used to assess SB, there are still concerns. First, the numerous measures of cognitive function currently in use are obfuscating the relationship between SB and cognition. The eight studies we reviewed used a total of 13 measures of cognitive function. Specifically, the studies assessed memory by six different tests, executive function by four tests, processing speed by two methods, cognitive impairment by two methods, and global cognitive function by three methods. With such a wide variety of measures used to assess each domain of cognitive function, comparing study results is extremely difficult. Based on the heterogeneity of measures, we recommend future studies use the following instruments for each domain of cognition to allow comparisons across studies: 1) RI-48 for memory; 2) Trail Making Task for executive function; 3) immediate word recall for processing speed; 4) the Rey-Osterriety Complex Figure Copy and Recall Test for perceptual organization and planning; and 5) the MoCA [457] for global cognition.

In addition, the numerous domains of cognition being assessed (i.e., global cognition, memory, executive function, etc.) prevents comparisons of study results. Few studies tested similar domains of cognition, and thus it is unclear if SB is associated with decreases in global cognitive function, several different domains of cognition, or just a single domain. Future studies therefore need to first determine which domains of cognitive function decrease with increased SB. One means of
potentially assessing all domains of cognitive function concomitantly would be the use of the NIH toolbox [461], which could independently examine the associations of SB with memory, executive function, and so forth.

Several of the measures used to assess cognitive function in these studies also lacked evidence of validity or reliability, and thus the conclusions may not be valid for the construct the authors planned to investigate [84]. For example, Hamer and Stamatakis used a memory test (i.e., delayed word recall) without evidence of validity or reliability [156]; thus rather than measuring memory, the test may be related to another construct, such as executive function.

While there are some issues with measurement of cognitive function in these studies, our preliminary findings suggest SB is negatively associated with memory, executive function, and global cognition. These findings suggest SB has an inverse association with cognition compared to exercise training and MVPA. MVPA—as well as AT and RT—are well documented to affect multiple domains of cognitive function [106]. Furthermore, MVPA and exercise training are established as an all-cause dementia prevention measure which could reduce the incidence of all-cause dementia by as many as one million cases worldwide [509]. Given this information, SB may be adversely associated with the same neurophysiological pathways as MVPA and exercise.

2.4.5 Study quality

The STROBE checklist for observational studies is designed to ensure important information on study design is available so readers of research can follow what was planned, what was done, what was found, and what conclusions can be drawn [473]. This information is an important component
for systematic reviews [510, 511]; however when components required by the STROBE guidelines are absent, the conclusions which can be drawn from these studies suffer.

The quality of studies we reviewed varied greatly with several of the studies showing multiple flaws in reporting. Only one study [475], met all criteria of the STROBE and several studies were missing multiple criteria. Issues such as sampling bias, selection bias, recall bias and detection bias may therefore have inflated the results of these studies. We therefore recommend future investigations on how SB is associated with cognitive function firmly adhere to the STROBE guidelines.

Finally, the lack of a sample size calculation by any of the studies we reviewed is an important concern. Sample size calculations for observational studies require a compromise between balancing the needs of power, economy and timeliness [512]. Failure to attain a sample size with enough power inevitably leads to type II error; however equally erroneous is using a sample size that is “too big” that detects an effect of little scientific importance [513]. For example, one study we reviewed included well over 6,000 participants [156], which may have accounted for the significant—albeit small—results.

2.4.6 Recommendations

Current PA guidelines offer a brief policy recommendation on SB—avoid it as much as possible [258, 439]; however, in order to best promote healthy cognitive aging, an empirically derived public health message is still needed. Thus, we have developed healthy cognitive aging guidelines for SB which are in-line with current evidence and recommendations [258, 265, 471, 514]. We
therefore recommend all adults should: 1) avoid sedentary time wherever possible; 2) limit discretionary sitting time to <2 hours/day; 3) stand up and move after 30 minutes of uninterrupted sitting; and 4) increase LPA (i.e., standing and light walking) to >2 hours/day by substituting these activities for sedentary time (e.g., stand while watching television).

Combating a sedentary lifestyle—and associated cognitive declines—also requires an emphasis on encouraging adults to engage in ≥150 minutes/week of MVPA. Regular MVPA is a pillar of healthy cognitive aging, with current evidence suggesting ≥150 minutes/week of MVPA reduces the risk of AD by 38% [515]. Moreover, empirical evidence has found a consistent relationship between MVPA and cognitive function [156]. Given the current evidence, we recommend all adults limit discretionary SB to <2 hours/day and concomitantly engage in ≥150 minutes/week of MVPA. Meeting these recommendations may best promote healthy cognitive aging and could reduce the incidence of all-cause dementia by more than one million cases worldwide [509].

2.4.7 Limitations and future directions

This review only investigated observational studies on how SB is associated with cognitive function; however, to our knowledge this is the first systematic review to evaluate the evidence. There may also be a publication bias which limits the generalisability of our findings; however this limitation is inherent in all systematic reviews. Our systematic review located only eight studies, but our findings do show a consistent relationship such that SB is associated with poorer cognitive function. Although all four high quality studies found SB is associated with poorer cognition [474-477], more high quality studies are needed before estimates can be made about the attributable risk of SB to cognitive impairment and all-cause dementia.
Given this area of research is still developing, our study only provides an initial platform for examining the association of SB with cognitive impairment and all-cause dementia. Our preliminary recommendations for healthy cognitive aging are therefore broadly consistent with current policy [258, 265, 471, 514], and may need to be refined as more evidence emerges.

Dementia is also a complex disease which has several forms including AD and vascular dementia, which have vastly different aetiologies. While the mechanisms may be different by which the different sub-types of dementia occur, there are certainly similarities in terms of risk factors. For example, Laurin and colleagues found increased MVPA was associated with reduced risks of cognitive impairment and dementia of any type [515]. Thus, our preliminary findings suggest reduced cognitive function and increased all-cause dementia risk are associated with a sedentary lifestyle. Future studies should determine the associations of SB with different types of dementia.

Related to this issue, different types of SB may have different associations with cognitive function. For example, there is some evidence that computer use may positively affect cognition [475-477]. However, only eight studies assessing SB were included in our review—and only three studies assessed computer use as an exposure variable [475-477]—and thus it is difficult to make comparisons and draw conclusions at this time. Future studies are needed to determine how different sedentary activities moderate the relationship between SB and cognitive function.

2.4.8 Conclusions
The current body of evidence suggests SB is negatively associated with cognitive function; however, the associations between SB and cognitive function are complex and largely dependent on both the exposure variable and outcomes assessed. Nonetheless, our findings suggest reducing discretionary sedentary time to <2 hours/day and concomitantly engaging in $\geq 150$ minutes/week of MVPA may best promote healthy cognitive aging.
Chapter 3: Cross-sectional relationships of physical activity and sedentary behavior with cognitive function in older adults with probable Mild Cognitive Impairment


3.1 Introduction

By 2030, there will be nearly one billion older adults worldwide [13]. Since age is the greatest risk factor for dementia [464], the number of dementia cases is expected to increase substantially [15]. Pharmaceutical therapies to treat dementia are still in their infancy [516, 517], and thus reducing the risk of dementia—and potentially dementia incidence—requires the development of effective lifestyle-based strategies.

MCI represents a critical phase to intervene then, since it is a transitional stage between healthy cognition and dementia [17]. MCI is defined as cognitive decline greater than expected for age and education level which does not interfere with independence [18], and is associated with up to a 30% increased risk of developing dementia within 5 years [19]. By comparison, older adults without MCI develop dementia at a rate of 1% to 2% within 5 years [20]. Providing effective strategies to maintain cognitive health during this transition period might slow the conversion to dementia.

One potential strategy is PA—a behavior associated with both cognitive and physical health [106]. High levels of PA are prospectively linked to lower incidence of MCI and dementia [102, 153,
and an estimated 17.7% of AD cases could be prevented through PA [468]. PA also has multidimensional health benefits including reduced risk of mortality, and chronic diseases such as type 2 diabetes mellitus and cardiovascular disease [101, 520, 521]. Given the importance of PA for health, current recommendations for older adults suggest 30 minutes of MVPA (in bouts as brief as 10 minutes of moderate intensity) 5 days/week [90, 439]. Unfortunately, >95% of older adults are physically inactive (i.e., do not engage in ≥150 minutes/week of MVPA) and thus fall short of these recommendations [96].

While the importance of PA (particularly MVPA) for cognitive health is well established, less is known about the impact of SB on both physical and cognitive health. SB is any behavior which incurs ≤1.5 METs and includes activities such as sitting, television watching, and lying down; MVPA is any behavior incurring ≥3.0 METs [8]. Recent evidence suggests SB may be associated with poorer cognitive function and increased risk of cognitive impairment, although epidemiological data are needed to confirm this association [6, 7]. Accumulating evidence also suggests SB is associated with numerous chronic diseases including type 2 diabetes mellitus and cardiovascular disease [265, 266]. These chronic diseases are concomitantly linked with increased risk of cognitive decline and dementia [268, 270], providing further evidence that high SB is a risk factor for cognitive health. Due to the increasing evidence suggesting PA and SB are associated with cognitive health, older adults are recommended to limit discretionary SB to <2 hours/day; avoid sitting for longer than 30 minutes without standing; and concomitantly increase MVPA to ≥150 minutes/week [522].
Physical therapists are in a unique position to help influence both PA and SB. The potent position of clinicians to maximize patient compliance by influencing behavior is why the US Preventive Task Force has recommended clinicians provide PA counselling since 1989 [523, 524]. In addition, RCTs using activity counselling among older adults in a primary care setting have been highly successful at increasing patient PA [525, 526]. As such, these data further illustrate the importance of activity counselling in the clinical setting and suggest even brief questions about patient activity levels can have demonstrable improvements on patient health outcomes, such as cardiovascular disease and mortality risk [527]. Thus, as an important step to promote older adult cognitive health, clinicians should consult their older adult patients about their PA and SB.

Since the current evidence suggests PA and SB are important for healthy cognitive aging, a next step—given the window of opportunity to intervene for people with MCI—is an analysis of PA and SB differences between people with MCI and those without MCI. Importantly, it is unclear whether people with MCI engage in different amounts of PA and SB than their peers without MCI and whether the associations of PA and SB with cognitive function are the same or different between older adults with MCI and those without MCI. Indeed, because of underlying neurobiological differences between older adults with MCI and those without MCI [2], a functional weakening in the relationships of health behaviors with cognitive function may occur in MCI [296]. However, data are still needed showing the associations of PA and SB with cognitive function attenuate based on MCI status in order to confirm this hypothesis. Answering these questions may help inform clinicians concerned about the cognitive health of their older adult patients, and help determine which of their older adult patients may see the greatest benefits to cognitive health from PA and SB counselling.
To address these gaps in knowledge, we first investigated differences in MVPA and SB between older adults with probable MCI and those without. In addition, we determined whether the relationships of MVPA and SB with cognitive function differed based upon MCI status.

3.2 Methods
All participants provided written informed consent. Ethics approval for this study was obtained from the Vancouver Coastal Health Research Institute and the University of British Columbia’s Clinical Research Ethics Board (H14-01301).

3.2.1 Protocol
For this cross-sectional study, we recruited and collected data between August of 2014 and June of 2016. At study entry, we ascertained general health, demographics, socioeconomic status, and education by questionnaire. Subsequently, we screened participants for MCI using the MoCA, with a score of <26 indicating probable MCI status [457]. Participant MVPA and SB were then observed for ≥4 days using the MW8. Following MW8 observation, we measured cognitive function for all participants using the ADAS-Cog Plus [454].

3.2.2 Participants
Participants were recruited from Vancouver, British Columbia by advertisements placed in local community centres, newspapers, and word of mouth referrals. Potential participants were considered eligible if they met the following 3 criteria: 1) men and women at least 55 years old and living in the greater Vancouver area; 2) scores of >24/30 on the MMSE [487]; and 3) ability
to read, write, and speak English with acceptable visual and auditory acuity. Participants were ineligible if they were diagnosed with dementia of any type, diagnosed with another type of neurodegenerative or neurological condition, taking medications that may negatively affect cognitive function, planning to participate in or currently enrolled in a clinical drug trial, or unable to speak as judged by an inability to communicate by phone. Of the 152 total potential participants who were recruited for this study, only 1 dropped out because of a transient ischemic attack unrelated to the study. Thus, our obtained sample size was 151 participants.

3.2.3 Measurement of moderate-to-vigorous physical activity and sedentary behaviour

We measured MVPA and SB using a valid and reliable measure among older adults, the MW8 [136]. Briefly, the MW8 is a uniaxial, wrist-worn accelerometer designed to observe acceleration ranging in magnitude from 0.01g to 8g with a frequency of 3–11 Hz. The filtered acceleration signal is digitized, and the magnitude is summed over a user-specified time interval. At the end of each interval, the summed value or activity “count” is stored in memory and the integrator is reset. For the current study, we used 60-second epochs [528].

At study entry, participants were fitted with the MW8. Details of the measurement protocol used for the MW8 can be found elsewhere [137]. Consistent with established protocol for MW8, participants wore the device on the non-dominant wrist for a period of ≥4 days [137], which is enough to provide reliable estimates of MVPA (ICC=.90, 95% CI=.86–.93) and SB (ICC=.91, 95% CI=.87–.94]). After collection, stored activity counts were downloaded and saved to an IBM-compatible computer (IBM SPSS, Chicago, Illinois) for subsequent data reduction and analysis.
3.2.4 Data Reduction

Data were analyzed using MotionWare 1.0.27 (CamNtech). Data prior to recorded wake time on the first full day of recording were manually removed in order to only investigate full 24-hour recordings of activity. Thus, a participant with 6 nights of sleep recorded had 5 full days of activity recorded. Each day of activity consisted of when the participant self-reported being awake and out of bed. Participant self-report was confirmed via event marker time stamps from MW8 or a consensus sleep diary which participants completed during the observation period.

A Microsoft Excel (Microsoft Corp, Redmond, Washington) macro written by RSF (Appendix D) was used to reduce data to the following 4 components: wake time for the participant by day; daily calculations of time the participant spent in SB (<1.5 METs) and MVPA (≥3.0 METs), as determined from the established cut-points [136]; average daily amounts of time spent in MVPA and SB; and average percentage of the day spent in MVPA (%MVPA) and SB (%SB). Non-wear time of MW8 was assessed as a period of consecutive zero counts ≥120 minutes in length [529]. In total, only 2 participants had periods of non-wear time (X̅=202 minutes/14 days; SD=107 minutes/14 days) according to this criterion. We therefore assumed participants did not remove the MW8 during observation.

3.2.5 Measurement of moderate-to-vigorous physical activity and sedentary behaviour 
bouts per day

We also examined the average 10+ min bouts/day of MVPA and 30+ min bouts/day of SB. A Python 2.7 code written by BKC was used to analyze the data (Appendix D). The script loaded each participant’s data from the Microsoft Excel spreadsheet into a Python data table. The script
then cleaned and separated the data into tables, one for each type of activity level (i.e., MVPA and SB). The data loaded into the tables was a sequence of 1’s and 0’s, wherein a “1” on an epoch meant an activity level of the corresponding threshold was detected, and a “0” meant the activity level corresponding to the threshold was not detected. The script then iterated through each day’s epochs with an incrementing counter, such that when a “1” was detected, the counter incremented. Once a break (i.e., “0”) was detected, the counter was then saved to another data table which kept track of the length of the bouts (i.e., streaks of activity at the corresponding activity threshold). The counter was then reset and began counting again when the next bout of activity was detected. Once the bout lengths were counted, we determined the average 10+ min bouts/day of MVPA and the average 30+ min bouts/day of SB for each participant.

3.2.6 Cognitive Function

We used the ADAS-Cog Plus to examine global cognitive function [454]. The ADAS-Cog Plus uses a multidimensional item response theory model that can flexibly utilize item scores from multiple cognitive assessment instruments to generate a global cognitive function score and standard error of measurement for that score [530]. Scores are defined by the ADNI cohort [455], wherein the mean score for cognitively healthy older adults is about −1.0, the mean for MCI is about 0.0, and the mean for dementia cases is about 1.0. Thus, higher scores indicate poorer cognitive performance. The ADAS-Cog Plus score was computed using the following 4 methods: the 13-item ADAS-Cog (validity: ICC= 0.80; test-retest: r= 0.93; [456]); Trail Making Tests A and B (validity: r= 0.36–0.93; test-retest: r= 0.67; [458]); Digit Span Forward and Backward (validity: r= 0.48–.85; test-retest: r= 0.62–0.82; [459]); and verbal fluency, consisting of animal
fluency and vegetable fluency (validity: \( r = 0.44–0.87 \); test-retest: \( r = 0.74 \); [459]). Detailed descriptions of the procedures used for these tests can be found elsewhere [456, 458, 459].

3.2.7 Data Analyses

We performed all of our statistical analyses using R version 3.5.1. Our complete statistical analyses can be found online in Appendix D (note: the published analyses were originally conducted in SPSS 22.0, but have been re-conducted in R version 3.5.1 for simplicity and reproducibility online). One participant was removed from our analyses as an outlier due to an ADAS-Cog Plus score which was >3 standard deviations above the mean score, suggesting the participant had possible severe cognitive impairment (MMSE=25; MoCA=17). Thus, our final sample size was 150. Given the non-normal distribution of average 10+ min bouts/day of MVPA, we transformed it by means of a natural log transformation which was used for all subsequent analyses as it most closely approximated a normal distribution. Because this was an exploratory analysis, we did not use a Bonferroni adjustment to account for multiple comparisons.

3.2.7.1 Participant characteristics based on probable MCI status

Means and standard deviations were calculated for all variables of interests based upon probable MCI status. To determine demographic differences based on probable MCI status, we performed independent samples t-tests for continuous variables and chi-square tests for categorical variables, using probable MCI status (yes/no) as the grouping variable. In addition, we performed analyses of covariance (ANCOVA) to determine differences in \%MVPA; 10+ min bouts/day of MVPA; \%SB; 30+ min bouts/day of SB; and cognitive function based on probable MCI status. These
models controlled for age and sex differences while using probable MCI status as the grouping variable.

3.2.7.2 Relationship of cognitive function with moderate-to-vigorous physical activity and sedentary behaviour based on probable Mild Cognitive Impairment status

We then examined the relationship of cognitive function with MVPA and SB for all participants. Multiple linear regression models were generated using ADAS-Cog Plus score as the dependent variable, while controlling for age, sex, and education. We generated four models, where the major independent variable of interest was %MVPA, 10+ min bouts/day of MVPA, %SB, or 30+ min bouts/day of SB. Beta estimates, model $R^2$, and $P$ values are presented for each model. We plotted the predicted relationship between each major independent variable and ADAS-Cog Plus score.

We then examined if the relationship of cognitive function with MVPA and SB differed based upon probable MCI status. Participants were stratified based upon probable MCI status and the same four multiple linear regression models were generated using ADAS-Cog Plus as the dependent variable, while controlling for age, sex, and education. We then performed $z$ tests to determine if beta estimates for MVPA and SB differed significantly based on probable MCI status. Beta estimates, model $R^2$, and $p$ values are presented for each model based upon probable MCI status; $z$ scores and $p$ values for comparing major independent variable estimates based on probable MCI status are also presented. We then illustrated the differences in the predicted relationship between each independent variable and ADAS-Cog Plus based upon cognitive status.

3.3 Results
3.3.1 Participant characteristics based on probable Mild Cognitive Impairment status

Participant characteristics are described in Table 3.1. The mean age was 71.11 years (SD=7.22 years) and 67.33% were female. Older adults without MCI had a mean MMSE score of 29.22 ± 0.10 (range=27–30), and a mean MoCA score of 27.19 ± 0.13 (range=26–30); older adults with probable MCI had a mean MMSE score of 28.65 ± 0.13 (range=25–30), and a mean MoCA score of 22.84 ± 0.23 (range=14–25). Older adults categorized with probable MCI were significantly older ($t=2.70$, $df=149$, $p=.008$) and more likely to be male ($\chi^2=5.22$, $p=.022$). While controlling for age and sex differences, participants with probable MCI also engaged in significantly less %MVPA ($F=4.81; df=1,150; p=.030$); fewer 10+ min bouts/day of PA ($F=7.94; df=1,150; p=.005$); and more 30+ min bouts/day of SB ($F=4.04; df=1,150; p=.046$); they also had poorer cognitive performance on the MMSE ($F=7.36; df=1,150; p=.007$), MoCA ($F=215.78; df=1,150; p<.001$), and ADAS-Cog Plus ($F=25.22; df=1,150; p<.001$).
Table 3.1 Participant characteristics

<table>
<thead>
<tr>
<th>Participant Characteristic</th>
<th>All participants (N=150)</th>
<th>Non-MCI Older Adults (N=69)</th>
<th>Probable MCI Older Adults (N=81)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.11 (7.22)</td>
<td>69.42 (6.37)</td>
<td>72.54 (7.62)</td>
<td>0.008</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td>101, 67.33%</td>
<td>53, 76.81%</td>
<td>59.26%</td>
<td>0.022</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School Diploma or less</td>
<td>28, 18.40%</td>
<td>11, 14.70%</td>
<td>17, 20.70%</td>
<td>0.303</td>
</tr>
<tr>
<td>Trade School</td>
<td>16, 11.20%</td>
<td>5, 7.40%</td>
<td>11, 13.40%</td>
<td></td>
</tr>
<tr>
<td>Some University</td>
<td>24, 15.80%</td>
<td>10, 14.70%</td>
<td>14, 17.10%</td>
<td></td>
</tr>
<tr>
<td>University Diploma or Higher</td>
<td>82, 54.60%</td>
<td>43, 63.20%</td>
<td>39, 48.80%</td>
<td></td>
</tr>
<tr>
<td>Retired (n, %)</td>
<td>116, 77.33%</td>
<td>54, 78.26%</td>
<td>62, 76.54%</td>
<td>0.802</td>
</tr>
<tr>
<td>Smoking Status (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>3, 2.00%</td>
<td>1, 1.45%</td>
<td>2, 2.47%</td>
<td>0.877</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>74, 49.33%</td>
<td>35, 50.72%</td>
<td>39, 48.15%</td>
<td></td>
</tr>
<tr>
<td>Never Smoked</td>
<td>73, 48.67%</td>
<td>33, 47.83%</td>
<td>40, 49.38%</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-Vigorous Physical Activity and Sedentary Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%MVPA*</td>
<td>10.25 (6.51)</td>
<td>12.07 (7.19)</td>
<td>8.69 (5.45)</td>
<td>0.030</td>
</tr>
<tr>
<td>LN(Average 10+ min bouts/day of MVPA)†</td>
<td>0.52 (0.44)</td>
<td>1.20 (1.45)</td>
<td>0.40 (0.36)</td>
<td>0.005</td>
</tr>
<tr>
<td>%SB‡</td>
<td>59.62 (12.00)</td>
<td>57.24 (12.38)</td>
<td>61.65 (11.35)</td>
<td>0.161</td>
</tr>
<tr>
<td>Average 30+ min bouts/day of SB</td>
<td>3.72 (1.83)</td>
<td>3.30 (1.73)</td>
<td>4.07 (1.85)</td>
<td>0.046</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Exam (MMSE)</td>
<td>28.91 (1.07)</td>
<td>29.22 (0.87)</td>
<td>28.65 (1.15)</td>
<td>0.007</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>24.84 (2.77)</td>
<td>27.19 (1.10)</td>
<td>22.84 (2.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADAS-Cog Plus§</td>
<td>-0.79 (0.65)</td>
<td>-1.11 (0.57)</td>
<td>-0.52 (0.59)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Average percent of the day spent in moderate-to-vigorous physical activity (MVPA)  
†Natural log transformation for Average 10+ Minute bouts/day of MVPA  
‡Average percent of the day spent in sedentary behaviour (SB)  
§Alzheimer’s Disease Assessment Scale Plus  
||F-test while controlling for age and sex
3.3.2 Association of cognitive function with moderate-to-vigorous physical activity and sedentary behaviour

Our models describing the relationship of cognitive function with MVPA and SB are described in Table 3.2. We found a significant relationship between higher %MVPA and better cognitive performance ($\beta = -0.017, p = .024$), and there was a marginal relationship between greater 10+ min bouts/day of MVPA and better cognitive performance ($\beta = -0.203, p = .070$). There was also a marginal relationship between higher %SB and poorer cognitive performance ($\beta = 0.007, p = .089$). Finally, we found a significant association between greater 30+ min bouts/day of SB and poorer cognitive performance ($\beta = 0.061, p = .016$). These relationships are illustrated in Figure 3.1.

Table 3.2 Association of sedentary behaviour and physical activity with Alzheimer’s Disease Assessment Scale Plus score

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>*Model $R^2$</th>
<th>$\Delta R^2$ due to IV</th>
<th>IV $\beta$ value</th>
<th>IV p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Activity (PA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%MVPA†</td>
<td>0.321</td>
<td>0.025</td>
<td>-0.017</td>
<td>0.024</td>
</tr>
<tr>
<td>LN(Average 10+ min bouts/day of MVPA)‡</td>
<td>0.312</td>
<td>0.016</td>
<td>-0.203</td>
<td>0.070</td>
</tr>
<tr>
<td><strong>Sedentary Behaviour (SB)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%SB§</td>
<td>0.311</td>
<td>0.014</td>
<td>0.007</td>
<td>0.089</td>
</tr>
<tr>
<td>Average 30+ min bouts/day of SB</td>
<td>0.324</td>
<td>0.027</td>
<td>0.061</td>
<td>0.016</td>
</tr>
</tbody>
</table>

DV= ADAS-Cog Plus score

*Models controlling for age, sex, and education
† Average percent of the day spent in MVPA
‡ Log transformed average 10+ min bouts/day of MVPA
§ Average percent of the day spent in SB
Figure 3.1 Association of moderate-to-vigorous physical activity and sedentary behaviour with cognitive function

A) Association of percent of day spent in MVPA (%MVPA Time) with ADAS-Cog Plus Score; B) Association of number of 10+ minute bouts/day of MVPA with ADAS-Cog Plus Score; C) Association of percent of day spent in SB (%SB Time) with Alzheimer’s Disease Assessment Scale Plus score (ADAS-Cog Plus Score); D) Association of number of 30+ minute bouts/day of SB with ADAS-Cog Plus Score. Models controlled for age, sex, and education.
3.3.3 Relationship of cognitive function with moderate-to-vigorous physical activity and sedentary behaviour based on probable Mild Cognitive Impairment status

Table 3.3 describes the relationship of cognitive function with MVPA and SB based on probable MCI status. For older adults without MCI, higher %MVPA and greater 10+ min bouts/day of MVPA were associated with better cognitive performance ($\beta = -0.022$ [$p = .024$] and $\beta = -0.286$ [$p = .046$], respectively). However, neither MVPA characteristic was associated with cognitive performance for older adults categorized with probable MCI. In addition, the beta estimates for %MVPA ($z = 2.412$, $p = .016$) and 10+ min bouts/day of MVPA ($z = 1.986$, $p = .047$) differed significantly based on probable MCI status.

We also found higher %SB was associated with poorer cognitive performance for participants without MCI ($\beta = 0.012$, $p = .038$); there was a marginal relationship between greater +30 min bouts/day SB and poorer cognitive performance for participants without MCI ($\beta = 0.075$, $p = .064$). By comparison, there was no relationship for either SB characteristic with cognitive performance for older adults categorized with probable MCI. Finally, the relationship of %SB with cognitive performance was marginally different based on probable MCI status ($z = 1.536$, $p = .125$). These relationships are illustrated in Figure 3.2.

3.4 Discussion

Our results suggest older adults with probable MCI engage in less MVPA and more SB compared with adults without MCI. In addition, the relationship of MVPA and SB (to a lesser degree) with cognitive function differs by cognitive status such that MVPA and SB are only associated with cognitive function among participants without MCI. We now provide potential explanations for
Table 3.3 Association of moderate-to-vigorous physical activity and sedentary behaviour with Alzheimer’s Disease Assessment Scale Plus score based on probable Mild Cognitive Impairment (MCI) status

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Non-MCI (N= 69)</th>
<th>Probable MCI (N=81)</th>
<th>IV β value differences based on probable MCI status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model R²</td>
<td>ΔR² due to IV</td>
<td>IV β value</td>
</tr>
<tr>
<td>Physical Activity (PA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%MVPA†</td>
<td>0.209</td>
<td>0.066</td>
<td>-0.022</td>
</tr>
<tr>
<td>LN(Average 10+ min bouts/day of MVPA)‡</td>
<td>0.195</td>
<td>0.052</td>
<td>-0.286</td>
</tr>
<tr>
<td>Sedentary Behaviour (SB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%SB§</td>
<td>0.199</td>
<td>0.056</td>
<td>0.012</td>
</tr>
<tr>
<td>Average 30+ min bouts/day of SB</td>
<td>0.188</td>
<td>0.045</td>
<td>0.075</td>
</tr>
</tbody>
</table>

DV= ADAS-Cog Plus Score  
*Models controlling for age, sex, and education  
† Average percent of day spent in MVPA  
‡ Log Transformed Average 10+ min bouts/day of MVPA  
§ Average percent of day spent in SB
Figure 3.2 Association of moderate-to-vigorous physical activity and sedentary behaviour with cognitive function based on the presence of Mild Cognitive Impairment

A) Association of percent of day spent in MVPA (%MVPA Time) with ADAS-Cog Plus Score; B) Association of number of 10+ minute bouts/day of MVPA with ADAS-Cog Plus Score. Models controlled for age, sex, and education; C) Association of percent of day spent in SB (%SB Time) with Alzheimer's Disease Assessment Scale Plus score (ADAS-Cog Plus Score); D) Association of number of 30+ minute bouts/day of SB with ADAS-Cog Plus Score). Models controlled for age, sex, and education. Blue=Non-MCI Older Adults; Red=MCI Older Adults.
these findings, as well as discuss how these findings can be applied to clinical practice.

3.4.1 Differences in physical activity and sedentary behaviour by cognitive status—does activity level change because of Mild Cognitive Impairment conversion?

Previous studies suggest low PA and high SB are both risk factors for cognitive impairment in later life [474, 522]; however, our study is the first to show that older adults with probable MCI are less active and more sedentary than their cognitively healthy peers. One potential explanation is younger adults at high risk for MCI in later life—due to lower PA and higher SB—continue to be less active and more sedentary into older adulthood, often becoming cognitively impaired as they age. Indeed, the current evidence suggests that PA and SB patterns worsen from childhood into young adulthood and then stabilize from middle adulthood onward [531]. It is therefore plausible that older adults with MCI are less active and more sedentary throughout their adult lives, and this behavior has continued into older adulthood.

It is also plausible that a reciprocal association is present, such that conversion to MCI influences PA and SB. In particular, this effect might occur through diminished executive function [19, 36, 482]. Briefly, executive function is a broad term used to define planning and problem-solving and is known to significantly decline with age [532, 533]. Loss of executive function capability has been shown to negatively impact older adult independence and functionality [534-536]. Increasing evidence also suggests PA and SB have a bidirectional relationship with executive function such that changes in executive function can predict changes in activity levels, and vice versa [537-539]. Thus, older adults living with MCI may have impaired decision making about engaging in PA or SB, due to impaired executive function capabilities.
3.4.2 Differences in the relationships of physical activity and sedentary behaviour with cognitive function by Mild Cognitive Impairment status—are there underlying differences in the Mild Cognitive Impairment brain?

To our knowledge, this is the first study to report differences in the relationships of MVPA and SB with cognitive function based upon cognitive status. One explanation is there might be a minimum threshold of MVPA and/or a maximum threshold of SB required to elicit a relationship with cognitive function. As discussed previously, older adults with probable MCI engaged in less PA and more SB than adults without MCI. As such, older adults with MCI may not meet a minimum threshold level of PA—or may exceed a maximum threshold of SB—which may lead to non-significant associations between these health behaviors and cognitive function. This interpretation of our findings may help explain why exercise and PA interventions for older adults with MCI can lead to significant improvements in cognitive function [185, 201]. Potentially, exercise and PA interventions for older adults with MCI help ameliorate cognitive function by providing a necessary threshold level of PA and concomitant reduction in SB. By comparison, the effects of PA and exercise interventions on older adults without MCI appears to be less substantial [540], perhaps due to higher levels of basal activity in these adults.

An alternative explanation for our findings is the relationships of MVPA and SB with cognitive performance differ by MCI status because of underlying neurobiological differences between older adults with MCI and those without [541]. For example, compared to older adults without MCI, those with MCI have greater amounts of Aβ accumulation [39], accelerated atrophy in the medial temporal lobe [40], and decreased connectivity of the posterior cingulate gyrus and hippocampus.
with the whole brain [46]. These underlying changes in the MCI brain may potentially alter the relationships of health behaviors with cognitive function [2], leading to an attenuation—or functional weakening—of the relationships of MVPA and SB with cognitive function [296].

3.4.3 Clinical applications

The findings of our study are also applicable towards improving clinical practice. First, given that PA and SB can have important implications on older adult physical and cognitive health [106, 522], all clinicians should make a serious effort to counsel their patients on PA and SB [527]. While the health care system has serious potential as a tool for promoting changes in older adult PA and SB, its potential is not being fully realized in clinical practice [542]. A first step to utilizing this untapped potential to promote behavior change is for clinicians to track their older adult patients’ PA and SB using objective monitors, such as a pedometer or a FitBit. While activity trackers may not be feasible for some clinicians to use in their practice, clinicians should at the very least ask brief questions about activity during their consultations with older adult patients since it can have important implications on both the physical and cognitive health of older adults [543].

Second, our data suggest that PA appears to have a stronger relationship with cognitive function than does SB. A recently published systematic review examining the relationship of SB with later life cognitive decline found that in order to best promote healthy cognitive aging, older adults should limit their SB and concomitantly increase their MVPA to ≥150 minutes/week [522]. In order to best promote healthy cognitive aging, it may thus be prudent at this time for clinicians to focus on ensuring their older adult patients obtain this threshold level of PA, and to advise their
patients to limit SB. Over 95% of older adults are underactive, and thus the greatest benefits to older adult physical and cognitive health may occur by increasing PA.

While the main findings of our study are complex and require future investigation, the recommendations highlighted above are practical for both older adults with MCI, and those without. We therefore suggest clinicians who are concerned about their older adult patients’ cognitive health should track patient activity levels with objective monitors, if possible, and at least ask simple questions about activity levels during patient visits; and encourage their older adult patients to engage in ≥150 minutes/week of MVPA and limit their SB as much as possible.

3.4.4 Limitations and future research

This study was cross-sectional and therefore cannot establish whether conversion to MCI attenuates the relationship of MVPA and SB with cognitive function. While MoCA is a standard measure for determining the cognitive status of older adults, MCI diagnosis is confirmed through a physician based on several criteria, including 1) medical history; 2) assessment of independence and activities of daily living; 3) subjective memory complaints; 4) neurological assessment; and 5) laboratory tests and neuroimaging [19, 36, 482]. Given that we did not confirm the diagnosis of MCI with a physician, we cannot conclude how many of the participants we classified as living with probable MCI would actually be diagnosed with MCI by a physician.

This was a secondary analysis of a study which did not obtain information on participant comorbidities, and thus we did not account for these potential confounders within our analyses.
Future studies will need to determine whether the associations of MVPA and SB with cognitive performance do indeed differ by cognitive status when accounting for comorbid conditions.

Our findings may have been influenced by an overlap of the constructs of MVPA and SB. Specifically, our MVPA and SB data had a medium-sized negative correlation ($r = -0.515$); however, a recent systematic review has also concluded that total PA and total SB have a modest to medium sized correlation [10].

While we used a measure of MVPA and SB which has good evidence of validity and reliability within this population [136, 137], given that we previously calibrated this device for MVPA and SB using this sample of older adults, the MW8 may still have over- or under-estimated participant MVPA and SB. We therefore suggest that future investigations examine the concurrent validity of the MW8 against another type of objective measurement tool (preferably a hip accelerometer; [111, 122]) and examine whether the findings reported in this manuscript can be replicated in other samples using other types of objective measures. We only measured one intensity level of PA (i.e., MVPA), and thus our conclusions about the cross-sectional relationships between PA and cognitive function in older adults with MCI may be different when accounting for LPA (i.e., 1.5-2.9 METs; [544]).

Future intervention research will also be needed to determine the minimum effective dose of PA—or SB—necessary for maintaining or improving cognitive function, and how this might differ by MCI status. In addition, future research will need to examine whether the relationships of MVPA and SB with cognitive function differ by MCI status due to underlying neurobiological changes.
3.4.5 Conclusions

This study found that older adults with probable MCI engage in less MVPA and more SB than older adults without MCI. Our results also suggest the relationships of MVPA and SB with cognitive function differ by probable MCI status. Future investigations should examine if a threshold amount of PA and SB is required to maintain cognitive health in older adults, or if underlying neurobiological changes associated with MCI alter the relationships of PA and SB with cognitive function.
Chapter 4: The independent associations of physical activity and sleep with cognitive function in older adults


4.1 Introduction

Maintaining older adult cognitive health is a prominent public health challenge of the 21st century, as one new case of dementia is detected every 4 seconds [1]. Age is the number one risk factor for dementia [464], and as the aging population grows [465], so too will the number of dementia cases. While there is not yet a pharmaceutical cure for dementia, non-pharmaceutical approaches may help reduce dementia risk [2]. As such, lifestyle and behavioural strategies are an important line of scientific inquiry for maintaining older adult cognitive health [545].

One strategy is increasing older adult PA, which has positive benefits on both physical and cognitive health [106]. Importantly, evidence suggests regular PA of ≥3.0 METs (i.e., MVPA) can reduce the risk of dementia by up to 28% [156]. While it is promising that meeting current PA guidelines of ≥150 minutes/week of MVPA may help maintain cognitive health throughout life [95], most older adults fall short of these recommendations [96]. Thus, increasing older adult PA has become a growing public health priority since it could help prevent up to 18% of all AD cases [468].

Current evidence suggests PA can impact cognitive health through multiple mechanisms [170], including stimulating neurogenesis (i.e., the creation of new neurons) and cerebral angiogenesis.
(the creation of new blood vessels in the brain). The precise physiological mechanism by which PA improves cognitive health is still under investigation, but it is clear that PA increases cellular proliferation, dendritic complexity, and dendritic spine density in the dentate gyrus of the hippocampus [227-230]. These adaptations in cytoarchitecture also occur in older animals [231-233, 546], suggesting the importance of PA for cognitive health throughout life. In addition to the benefits of PA for maintaining cognitive health, animal models have also experimentally shown that PA down-regulates inflammatory factors which are associated with the progression of AD [239, 240]. Specifically, transgenic mice given access to a running wheel have significantly reduced Aβ levels in their frontal cortex [239], and reduced pro-inflammatory markers IL-1β and TNF-α [240]. Both of these inflammatory markers are associated with increased Aβ load and have been linked to AD progression [242, 547].

Another promising strategy for promoting cognitive health is improving older adult sleep quality. Sleep complaints are common among older adults, with more than half of adults over 65 years reporting at least one chronic sleep complaint—the most common being the inability to stay asleep at night [323]. Changes in sleep quality are a normal consequence of aging [321]. However, poor sleep is prevalent and predictive of cognitive decline in older adults [345]. Unfortunately, while effective cognitive-behavioural interventions are available for poor sleep [366, 548], few people utilize these treatments [549].

Evidence suggests poor sleep can have serious consequences on cognitive function [326]. The observed neurocognitive impairments which are a consequence of poor sleep are attributable to suboptimal prefrontal cortical functionality [339, 340]. Importantly, the prefrontal cortex is the
principal cortical area involved with higher-order cognitive function [404, 550, 551]. Coupled with these data suggesting poor sleep can impair cognitive function is the growing body of evidence that poor sleep is not only more prominent among individuals with AD, but also increases the risk of developing AD [341]. Animal models have experimentally shown 1) increasing cortical Aβ, a key indicator of AD pathophysiology, increases sleep fragmentation [351]; 2) decreasing sleep quality and increasing wake-time escalates Aβ production and corresponding cortical deposition [352]; and 3) sleep promotes the clearance of extracellular Aβ which accumulates during wake-time [356]. Collectively, these results suggest sleep is a critical pathway through which the brain appears to maintain cognitive health. When this pathway is disrupted, a vicious cycle of accelerating AD progression may occur—wherein poor sleep causes an increase in AD progression, and vice-versa [9].

Importantly, PA has long been thought to help improve poor sleep [365]. Epidemiological studies have consistently found people believe PA improves their sleep, and people with higher PA level report sleeping better compared to more sedentary individuals [11]. While the reasons for why PA and sleep are related are still unclear, current evidence suggests three possible explanations [11, 364]. One theory suggests that since negative affective states (i.e., depressive symptoms and anxiety) contribute to poor sleep [366], the antidepressant and anxiolytic effects of PA explain the relationship between sleep and PA [367, 368]. Another hypothesis suggests better weight regulation through increased PA may be associated with better sleep quality [370], since obesity is related to poorer sleep quality [369]. A third hypothesis suggests that since poor physical function is associated with poorer sleep quality in older adults [372], and PA is associated with
improved physical function [371], PA may be related to better sleep quality through its effect on physical function.

While these preliminary hypotheses are interesting, the current evidence for a relationship between PA and sleep quality is largely based on self-reported PA and sleep quality [11, 365], which can yield vastly different measurements from objective reality [286, 373]. Since PA and sleep quality may be associated with each other and with cognition, investigating the relationships PA and sleep quality have with cognitive function should not be performed in isolation. For example, it is plausible that PA does not independently predict cognitive function, but influences cognition through sleep (or vice-versa). In order to address these questions regarding the independent associations of PA and sleep quality with older adult cognitive function, and the relationship of PA with sleep quality, it is necessary to examine objective PA and objective sleep quality concomitantly [136, 137].

This study therefore addresses the current gaps in the literature by examining whether 1) PA is associated with better cognitive performance independently of sleep quality; 2) sleep quality is associated with better cognitive performance independently of PA; and 3) whether PA is associated with sleep quality.

**4.2 Methods**

Ethical approval for this study was obtained from the Vancouver Coastal Health Research Institute and the University of British Columbia’s Clinical Research Ethics Board (H14-01301). All participants provided written informed consent.
4.2.1 Protocol

For this cross-sectional study, we recruited and collected data between August 27, 2014 and April 27, 2016. At study entry, we ascertained general health, demographics, socioeconomic status, and education by questionnaires. During this initial session, we measured subjective sleep quality using the PSQI [299]. Participants’ PA and sleep were then observed for 14 days using the MW8. Following MW8 observation, we measured cognitive function using the ADAS-Cog Plus [454].

4.2.2 Participants

Participants (N= 157; aged 55+ years) were recruited from Vancouver, British Columbia by advertisements placed in local community centres, newspapers, and word of mouth referrals. Participants were included if they met the following criteria: 1) men and women 55+ years of age living in the Metro Vancouver area; 2) scored >24/30 on the MMSE [487]; and 3) able to read, write, and speak English with acceptable visual and auditory acuity. Participants were excluded if: 1) diagnosed with dementia of any type; 2) diagnosed with another neurodegenerative or neurological condition; 3) taking medications which may negatively affect cognition; 4) planning to participate or currently enrolled in a clinical drug trial; or 5) unable to speak as judged by an inability to communicate by phone.

4.2.3 Subjective measurement of sleep quality

We measured subjective sleep quality using the PSQI [299]. This 19-item questionnaire assesses sleep quality using subjective ratings for 7 different components (i.e., sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleep medication; and daytime
dysfunction). Participants answer the questionnaire retrospectively, as the questionnaire surveys sleep components spanning the previous month. The questionnaire has good evidence of validity and reliability [301, 453].

### 4.2.4 Objective measurement of physical activity and sleep

We measured PA and sleep using MW8, a uni-axial, wrist-worn accelerometer with evidence of validity and reliability for use among older adults [136, 137]. For the current study, we used 60 second epochs which is consistent with current guidelines for estimating both PA and sleep [452, 528, 552], and the capabilities of the MW8 to measure sleep and PA concurrently. Participants were fitted with the MW8 actigraphy unit and provided detailed information on its features (i.e., the light sensor, event marker button, and status indicator). Participants were instructed to press the event marker button each night when they started trying to sleep; and again each morning when they finished trying to sleep. Consistent with established protocol for wrist-worn actigraphy, participants wore the MW8 on the non-dominant wrist for a period of 14 days [552, 553].

Participants were also given the 9-item CSD and asked to complete it each morning upon waking [302]. The responses from the CSD were used to confirm sleep windows identified by participants, as determined by the time stamped event markers. In cases where the event marker and CSD entry disagreed for the start time of the sleep window, we used light sensor data to determine “lights out”. Similarly, when the event marker and CSD entry disagreed for the end of the sleep window, we used “lights on” and activity onset to determine the end of the sleep window. Each day of PA consisted of when the participant reported being awake and out of bed (as per responses to the CSD and confirmed via event marker time stamps from MW8). If responses from the CSD entry
disagreed with the event markers entered by participants as the start of the day, we used light sensor data and activity onset to determine the start of the day. Similarly, when the event marker and CSD entry disagreed for the end of day (i.e., time spent trying to sleep), we used the light sensor data to determine the end of the day.

4.2.4.1 Data Reduction
Details of our data reduction procedure can be found elsewhere [137, 286]. Briefly, data were analyzed using MotionWare 1.0.27 (camntech). Data prior to recorded wake-time on the first full day of recording were manually removed in order to only investigate full 24-hour recordings of activity. Each day of activity consisted of when the participant self-reported being awake and out of bed. Participant self-report was confirmed via event marker time stamps from MW8.

The MotionWare software was used to estimate different parameters of sleep quality including: 
*fragmentation index*, *sleep efficiency* (time asleep expressed as a percentage of time in bed), *sleep duration* (total time spent sleeping), *sleep latency* (time between “lights out” and falling asleep), and *number of awakenings* (number of times the participant woke up during the sleep period). Briefly, fragmentation index is defined by MotionWare as the sum of 1) the total time spent sleeping categorized as *mobile* in the epoch-by-epoch *mobile/*immobile categorization expressed as a percentage of the time spent asleep; and 2) the number of *immobile* bouts which were \( \leq 1 \) minute in length expressed as a percentage of the total number of *immobile* bouts during time spent sleeping. The MW8 estimates of sleep quality have evidence of validity and reliability [298].
A Microsoft Excel macro written by RSF (Appendix D) was used to reduce PA data to daily calculations of time spent in MVPA (≥ 3.0 METs; [136]). We then calculated the percent of each day spent in MVPA (%MVPA). For example, if for a given day a participant was asleep from 12:00-6:00 AM, and went to bed the following evening at 10:00 PM, then we assumed that the participant spent 8 hours sleeping in a 24 hour period (i.e., 480 minutes). If this individual engaged in 100 minutes of MVPA, then the estimated %MVPA for that day would be:

\[
\frac{100 \text{ minutes of MVPA}}{960 \text{ minutes of wake time}} = 10.42\% \text{ of day spent in MVPA}
\]

The benefit of this approach is that it controls for differences in time which participants spent awake and out of bed.

We determined MW8 non-wear time using the criterion of Hutto and colleagues [529]. Briefly, this criterion suggests periods of consecutive zero counts ≥120 minutes in length be considered as non-wear time. Only two participants had periods of non-wear time (total non-wear times of 126 minutes and 278 minutes, respectively) according to this criterion. Thus, we assumed participants did not remove the MW8 during observation.

**4.2.5 Cognitive Function**

We used the ADAS-Cog Plus as a global measure of cognitive function [454]. The ADAS-Cog Plus uses a multidimensional item response theory model which can flexibly utilize item scores from multiple cognitive assessment instruments to generate a global cognitive function score and standard error of measurement for that score. Higher scores indicate poorer cognitive performance. The ADAS-Cog Plus score was computed using the 13-item ADAS-Cog [456], MoCA [457], Trail
Making Test A and B [458], Digit Span Forward and Backward [459], and verbal fluency [458]. Detailed descriptions of the procedures used for these tests can be found in Appendix C.

4.2.6 Statistical Analyses

We performed all of our statistical analyses using R version 3.3.1 using the lavaan 0.5-22 package. Our statistical code can be found in Appendix D. Because MW8 requires 14 days of continuous observation in order to provide a reliable estimate of both PA and sleep quality [137], we needed to exclude 11 participants with incomplete data (i.e., 6 participants did not complete 14 days of MW8 observation; 5 participants did not have complete cognitive data). We also excluded 9 participants from our analyses because they each had extreme outlier scores on variables of interest (i.e., >3 SD from the mean). Two participants had extreme average %MVPA (32.2% and 38.6% of day spent in MVPA), four participants had extreme average fragmentation indices (range: 66.14-71.85) and two had extreme average sleep latency (42 minutes and 72 minutes). In addition, we removed one participant from our analyses due to an extreme ADAS-Cog Plus score (1.52), which suggested possible severe cognitive impairment (MMSE = 25; MoCA = 17). Structural equation modeling is based on the general linear model, which assumes the data has a normal distribution; including these data would skew the distribution of our data and increase type I error [554]. Thus, our final sample size was 137.

Greater numbers of nocturnal awakenings decreases the accuracy of actigraphy [555], and this inaccuracy mostly affects measures of wakefulness during the night and sleep latency [452, 556]. As such, we included as a covariate the number of awakenings each night in each of our analyses of sleep efficiency (r= -0.62; p< 0.01), sleep fragmentation (r= 0.58; p< 0.01), and sleep latency
(r = 0.20; p < 0.01) in an effort to reduce error variance. Controlling for the number of awakenings also intuitively seems appropriate for determining the most accurate estimates of sleep fragmentation and sleep efficiency. For example, an individual could have 100 separate 1-minute bouts of wakefulness over the course of 8 hours spent in bed, or one bout of 100 minutes of wakefulness. Not controlling for the number of awakenings would provide identical estimates for sleep efficiency despite very different sleep architectures between these two hypothetical individuals. We expect there to be a similar example for sleep fragmentation, and thus controlling for the number of awakenings potentially provides the most accurate estimates of sleep fragmentation and sleep efficiency.

4.2.6.1 Preliminary Analyses

We calculated mean %MVPA, PSQI score, fragmentation index, sleep efficiency, sleep duration, and sleep latency over 14 days and then estimated bivariate correlations between all variables. Given our sample size of 137 participants and a two-tailed α = 0.01, we had 80% power to detect a two-tailed correlation with a small effect size (|ρ| = 0.28; [557]).

4.2.6.2 Main Analyses

Our main analyses used latent variable modeling to examine whether: 1) PA is associated with cognitive performance independently of sleep quality (i.e., PSQI score, fragmentation index, sleep efficiency, sleep duration, and sleep latency); 2) sleep quality is associated with cognitive function independently of PA; and 3) PA is associated with better sleep quality. The strength of this approach is that it allows researchers to examine latent variable models which provide separate estimates of relations of the latent construct with the measured variables used to estimate the latent
construct (i.e., the measurement model), and the relationships of the different latent constructs with each other, or with other outcome variables (i.e., the structural model; [558]). This allows examination of the relations among latent constructs which are corrected for biases attributable to random error and construct-irrelevant variance.

Our model is described in Figure 4.1. Briefly, we generated four separate models which each concomitantly examined:

1) The predictors of the latent construct of PA and the predictors of the specified latent construct of sleep quality (i.e., PSQI score, sleep fragmentation, sleep duration, sleep efficiency, or sleep latency).

2) The relationship of the latent construct of PA with cognitive function, independently of the specified construct of sleep quality.

3) The relationship of the specified latent construct of sleep quality with cognitive function, independently of latent construct PA.

4) The relationship of latent construct PA with the specified construct of sleep quality.

Latent construct PA was estimated from each daily estimate of %MVPA. We separately estimated latent constructs of sleep quality for PSQI score, sleep fragmentation, sleep efficiency, sleep duration, and sleep latency from daily estimates for the given measure of sleep quality. For example, the latent construct of sleep fragmentation was estimated from each daily estimate of
Figure 4.1 Hypothesized relationship between physical activity and sleep quality

Path A: Black dotted lines represent the relationship between covariates and PA, grey dotted lines represent relationship between covariates and sleep quality. Path B: Black line represents the relationship between PA and cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus). Path C: Grey line represents the relationship between sleep quality and cognitive performance on the ADAS-Cog Plus. Path D: Outlined double-arrow represents relationship between PA and sleep quality. *Note: Models examining the relationship of PA with 1) sleep fragmentation; 2) sleep efficiency; and 3) sleep latency were adjusted for the number of awakenings each night. Awakenings was included as a predictor of sleep quality, and as a covariate for the relationship between sleep quality and cognitive function.
fragmentation index over the 14 day measurement period. Manifest indicators for each daily estimate of %MVPA and/or sleep quality were fixed such that each day contributed an equal loading on the latent variable. In order to improve model fit, each daily estimate of %MVPA was allowed to correlate with the previous day’s estimate. Thus, %MVPA on the third day of measurement was allowed to correlate with %MVPA on the fourth day of measurement. We also used the same approach to improve model fit for each given measure of sleep quality, such that each daily estimate for a given measure of sleep quality was allowed to correlate with the previous day’s estimate. For example, sleep duration on the third day of measurement was allowed to correlate with sleep duration on the fourth day. In order to maintain parsimony and clarity, we generated a separate model for each sleep quality measure.

Each model thus concomitantly estimated the relationship of 1) PA and the specified latent construct of sleep quality from age, sex, use of sleep medication, and smoking status (Figure 4.1, Path A); 2) PA and ADAS-Cog Plus score controlling for age, sex, education, and the specified latent construct of sleep quality (Figure 4.1, Path B); 3) the specified latent construct of sleep quality and ADAS-Cog Plus score controlling for age, sex, education, and PA (Figure 4.1, Path C); and 4) PA and the specified latent construct of sleep quality (Figure 4.1, Path D). We generated model fit statistics for each of our four separate models (Appendix E). Acceptable goodness-of-fit (i.e., RMSEA < 0.10 and SRMR < 0.08) was determined using the criteria of Hooper, Coughlan and Mullen [559].

4.3 Results
4.3.1 Participant Characteristics
Table 4.1 provides participant characteristics. The mean age was 71.22 years (SD= 7.23 years) and 67.9% were female. Mean %MVPA was 9.91 (SD= 5.84), mean PSQI score was 7.29 (SD=3.99), and mean sleep duration was 402.41 minutes (SD= 46.90).

4.3.2 Preliminary Analyses
Bivariate and partial correlations are described in Table 4.2. Greater age was significantly associated with poorer ADAS-Cog Plus performance (r= 0.36; p<0.01), less %MVPA (r= -0.31; p<0.01), more fragmented sleep (r= 0.31; p<0.01), and longer sleep duration (r= 0.18; p= 0.04). Better ADAS-Cog Plus performance was associated with higher %PA (r= -0.28; p<0.01). However, ADAS-Cog Plus was not significantly associated with any measure of sleep quality. In addition, %MVPA was not significantly associated with any measure of sleep quality.

4.3.3 Main Analyses
The results of our latent variable analyses are described in Table 4.3. All models achieved acceptable levels of fit [75]. Model fit statistics can be found in Appendix E.

4.3.3.1 Association of physical activity, Pittsburgh Sleep Quality Index, and Alzheimer’s Disease Assessment Scale Plus
Predictors of our latent variable PA and latent variable PSQI are described in Figure 4.2A. Predictors for latent variable PA explained 18% of the variance, with greater age (β= -0.25; p<0.01) and female sex (β= -2.21; p= 0.02) associated with lower PA.
Table 4.1 Participant characteristics

<table>
<thead>
<tr>
<th>Participant characteristic (N= 137)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.22 (7.23)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>93, 67.9%</td>
</tr>
<tr>
<td>Smoking Status (n, %)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>2, 1.5%</td>
</tr>
<tr>
<td>Past Smoker</td>
<td>66, 48.2%</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>69, 50.4%</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
</tr>
<tr>
<td>University Graduate or Higher</td>
<td>74, 54.0%</td>
</tr>
<tr>
<td>Some University</td>
<td>23, 16.8%</td>
</tr>
<tr>
<td>Trade School</td>
<td>15, 10.9%</td>
</tr>
<tr>
<td>High School Graduate</td>
<td>19, 13.9%</td>
</tr>
<tr>
<td>Less than High School Graduate</td>
<td>6, 4.4%</td>
</tr>
<tr>
<td>Mini Mental State Exam (MMSE)(a)</td>
<td>28.94 (1.03)</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MoCA)(a)</td>
<td>24.88 (2.75)</td>
</tr>
<tr>
<td>Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus) score</td>
<td>-0.77 (0.65)</td>
</tr>
<tr>
<td>Percent of the day spent in MVPA (%MVPA)</td>
<td>9.91 (5.84)</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index (PSQI) score(b)</td>
<td>7.29 (3.99)</td>
</tr>
<tr>
<td>Sleep Fragmentation Index(c)</td>
<td>30.37 (5.62)</td>
</tr>
<tr>
<td>Sleep Efficiency (%)(c)</td>
<td>83.10 (3.20)</td>
</tr>
<tr>
<td>Sleep Duration (minutes)</td>
<td>402.41 (46.90)</td>
</tr>
<tr>
<td>Sleep Latency (minutes)(c)</td>
<td>5.70 (0.93)</td>
</tr>
</tbody>
</table>

\(a\) Maximum score of 30

\(b\) Maximum score of 21

\(c\) Adjusted for average awakenings each night
Table 4.2 Correlation matrix

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>PSQI Total Score</th>
<th>ADAS-Cog Plus</th>
<th>Mean %MVPA</th>
<th>Fragmentation Index&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sleep Efficiency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sleep Duration</th>
<th>Sleep Latency&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI Total Score</td>
<td>-0.08</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog Plus</td>
<td>0.36**</td>
<td>0.05</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean %MVPA</td>
<td>-0.31**</td>
<td>0.07</td>
<td>-0.28**</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragmentation Index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.31**</td>
<td>-0.02</td>
<td>-0.03</td>
<td>-0.15</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.07</td>
<td>-0.01</td>
<td>0.17</td>
<td>-0.14</td>
<td>-0.61**</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.18*</td>
<td>0.06</td>
<td>0.16</td>
<td>-0.03</td>
<td>-0.34**</td>
<td>0.64**</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sleep Latency&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.01</td>
<td>0.08</td>
<td>0.11</td>
<td>-0.03</td>
<td>0.15</td>
<td>-0.31**</td>
<td>-0.12</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Note*: PSQI= Pittsburgh Sleep Quality Index; ADAS-Cog Plus=Alzheimer’s Disease Assessment Scale Plus; %MVPA=Percent of the day spent in moderate-to-vigorous physical activity

* *p < 0.05; **p < 0.01;  <sup>a</sup>Adjusted for number of awakenings each night
Table 4.3 Structural equation model estimates ± s.e.

<table>
<thead>
<tr>
<th>Predictors of Physical Activity</th>
<th>Model 1 Pittsburgh Sleep Quality Index</th>
<th>Model 2 Sleep Fragmentation</th>
<th>Model 3 Sleep Efficiency</th>
<th>Model 4 Sleep Duration</th>
<th>Model 5 Sleep Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.25 ± 0.06**</td>
<td>-0.23 ± 0.06**</td>
<td>-0.23 ± 0.06**</td>
<td>-0.23 ± 0.06**</td>
<td>-0.23 ± 0.06**</td>
</tr>
<tr>
<td>Sex</td>
<td>-2.21 ± 0.95*</td>
<td>-2.18 ± 0.95*</td>
<td>-2.18 ± 0.95*</td>
<td>-2.18 ± 0.95*</td>
<td>-2.18 ± 0.95*</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>-0.76 ± 0.83</td>
<td>-0.79 ± 0.83</td>
<td>-0.80 ± 0.83</td>
<td>-0.80 ± 0.83</td>
<td>-0.80 ± 0.83</td>
</tr>
<tr>
<td>Use of Sleeping Medications</td>
<td>2.09 ± 1.34</td>
<td>2.15 ± 1.34</td>
<td>2.15 ± 1.34</td>
<td>2.15 ± 1.34</td>
<td>2.15 ± 1.34</td>
</tr>
</tbody>
</table>

| Predictors of Sleep Quality     |                                       |                           |                          |                        |                      |
| Age                             | 0.09 ± 0.01**                         | 0.36 ± 0.09**             | -0.05 ± 0.05             | 0.02 ± 0.01*           | 0.01 ± 0.05          |
| Sex                             | -1.11 ± 0.66                          | -1.74 ± 1.42              | 1.63 ± 0.76*             | 0.02 ± 0.14            | -1.35 ± 0.81         |
| Smoking Status                  | 0.44 ± 0.57                           | 1.29 ± 1.20               | 1.28 ± 0.65*             | 0.20 ± 0.13            | -0.52 ± 0.68         |
| Use of Sleeping Medications     | 5.63 ± 0.93**                         | -0.50 ± 1.93              | -0.55 ± 1.03             | 0.17 ± 0.20            | 2.28 ± 1.10*         |
| Average Number of Awakenings    | 0.90 ± 0.10**                         | -0.49 ± 0.05**            |                           |                        | 2.15 ± 1.34**        |

Relationships of Physical Activity and Sleep Quality with ADAS-Cog Plus

| Physical Activity | -0.03 ± 0.01** | -0.02 ± 0.01** | -0.02 ± 0.01 | -0.02 ± 0.01** | -0.02 ± 0.01* |
| Sleep Quality     | 0.00 ± 0.01    | -0.01 ± 0.01   | -0.01 ± 0.01* | -0.06 ± 0.06   | 0.02 ± 0.02     |

Covariance between Physical Activity and Sleep Quality

| -1.16 ± 1.56       | -3.26 ± 3.20   | -2.35 ± 1.73   | 0.07 ± 0.33     | -1.99 ± 3.16    |

Note: ADAS-Cog Plus= Alzheimer’s Disease Assessment Scale Plus

* p < 0.05; ** p < 0.01; a Adjusted for number of awakenings each night
Figure 4.2 Structural equation models exploring the relationship of physical activity with Pittsburgh Sleep Quality Index

Significant relationships and standardized estimates (p < 0.05; *p < 0.01) are displayed. Models have been simplified for clarity. Path A: Black dotted lines represent predictors of PA over 14 days. Grey dotted lines represent predictors of Pittsburgh Sleep Quality Index score. Path B: Black solid line represents the relationship of PA with cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus); controlling for age, sex, education, and Pittsburgh Sleep Quality Index score. Path C: Grey solid line represents the relationship of Pittsburgh Sleep Quality Index score with cognitive performance on the ADAS-Cog Plus; controlling for age, sex, education and PA. Path D: Outlined double-arrows represent the relationship between PA and Pittsburgh Sleep Quality Index score; standardized-betas and p-values are shown in box.
Predictors for latent variable of PSQI explained 26% of the variance, with age ($\beta= 0.09; p<0.01$) and use of sleep medication ($\beta= 5.63; p<0.01$) being associated with poorer sleep quality. Figure 4.2B describes the relationship between PA and cognitive performance, wherein greater PA was associated with better ADAS-Cog Plus Score independently of PSQI ($\beta= -0.03; p<0.01$). PSQI was not associated with ADAS-Cog Plus performance independently of PA (Figure 4.2C). In addition, there was no significant relationship between PA and PSQI (Figure 4.2D).

### 4.3.3.2 Association of physical activity, sleep fragmentation, and Alzheimer’s Disease Assessment Scale Plus

Figure 4.3A describes the predictors for latent variable PA and latent variable sleep fragmentation. Predictors for latent variable PA explained 16% of the variance, with greater age ($\beta= -0.23; p<0.01$) and female sex ($\beta= -2.18; p= 0.02$) associated with lower PA. Predictors for our latent variable of sleep fragmentation explained 45% of the variance, with age ($\beta= 0.36; p<0.01$) and average number of awakenings ($\beta= 0.90; p<0.01$) being associated with greater sleep fragmentation. Figure 4.3B illustrates the relationship between PA and cognitive performance, wherein greater PA was associated with better ADAS-Cog Plus Score independently of sleep fragmentation ($\beta= -0.02; p<0.01$). Figure 4.3C illustrates that there was no significant relationship between sleep fragmentation and ADAS-Cog Plus performance independently of PA. There was also no significant relationship between PA and sleep fragmentation (Figure 4.3D).
Figure 4.3 Structural equation models exploring the relationship of physical activity with sleep fragmentation

Significant relationships and standardized estimates ($p < 0.05$; *$p < 0.01$) are displayed. Models have been simplified for clarity. **Path A**: Black dotted lines represent predictors of PA over 14 days. Grey dotted lines represent predictors of sleep fragmentation over 14 days. **Path B**: Black solid line represents the relationship of PA with cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus); controlling for age, sex, education, and sleep fragmentation. **Path C**: Grey solid line represents the relationship of sleep fragmentation with cognitive performance on the ADAS-Cog Plus; controlling for age, sex, education, awakenings, and PA. **Path D**: Outlined double-arrows represent the relationship between PA and sleep fragmentation; standardized-betas and $p$-values are shown in box.
4.3.3.3 Association of physical activity, sleep efficiency, and Alzheimer’s Disease Assessment Scale Plus

In Figure 4.4A, we describe the predictors for latent variable PA and sleep efficiency. Briefly, predictors for PA explained 16% of the variance, with greater age ($\beta = -0.23; p<0.01$) and female sex ($\beta = -2.18; p= 0.02$) associated with lower PA. Predictors for sleep efficiency explained 33% of the variance, with average number of awakenings ($\beta = -0.49; p<0.01$) being associated with poorer sleep quality; female sex ($\beta = 1.63; p= 0.03$) and smoking status ($\beta = 1.28; p= 0.05$) were associated with higher sleep efficiency. Figure 4.4B illustrates that higher PA was marginally associated with better performance on ADAS-Cog Plus independently of sleep efficiency ($\beta = -0.02; p= 0.06$). Figure 4.4C describes the relationship between sleep efficiency and cognitive performance, where greater sleep efficiency was significantly associated with better performance on ADAS-Cog Plus independently of PA ($\beta = -0.01; p= 0.04$). However, there was no significant relationship between PA and sleep efficiency (Figure 4.4D).

4.3.3.4 Association of physical activity, sleep duration, and Alzheimer’s Disease Assessment Scale Plus

Figure 4.5A describes the predictors for latent variable PA and latent variable sleep duration. Predictors for latent variable PA explained 16% of the variance, with greater age ($\beta = -0.23; p<0.01$) and female sex ($\beta = -2.18; p= 0.02$) associated with lower PA. Predictors for latent variable of sleep duration explained 6% of the variance with greater age associated with longer sleep duration ($\beta = 0.02; p= 0.03$). Figure 4.5B illustrates the relationship between PA and cognitive performance, wherein higher PA was significantly associated with better performance on ADAS-Cog Plus independently of sleep duration ($\beta = -0.02; p<0.01$). Sleep duration was not significantly
Figure 4.4 Structural equation models exploring the relationship of physical activity with sleep efficiency

Significant relationships and standardized estimates ($p < 0.05$; *$p < 0.01$) are displayed. Models have been simplified for clarity. **Path A:** Black dotted lines represent predictors of PA over 14 days. Grey dotted lines represent predictors of sleep efficiency over 14 days. **Path B:** Black solid line represents the relationship of PA with cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus); controlling for age, sex, education, and sleep efficiency. **Path C:** Grey solid line represents the relationship of sleep efficiency with cognitive performance on the ADAS-Cog Plus; controlling for age, sex, education, awakenings and PA. **Path D:** Outlined double-arrows represent the relationship between PA and sleep efficiency; standardized-betas and p-values are shown in box.
Figure 4.5 Structural equation models exploring the relationship of physical activity with sleep duration

Significant relationships and standardized estimates (p < 0.05; *p < 0.01) are displayed. Models have been simplified for clarity. Path A: Black dotted lines represent predictors of PA over 14 days. Grey dotted lines represent predictors of sleep duration over 14 days. Path B: Black solid line represents the relationship of PA with cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus); controlling for age, sex, education, and sleep efficiency. Path C: Grey solid line represents the relationship of sleep duration with cognitive performance on the ADAS-Cog Plus; controlling for age, sex, education and PA. Path D: Outlined double-arrows represent the relationship between PA and sleep duration; standardized-betas and p-values are shown in box.
associated with ADAS-Cog Plus performance independently of PA (Figure 4.5C), and there was no significant relationship between PA and sleep duration (Figure 4.5D).

4.3.3.5 Association of physical activity, sleep latency, and Alzheimer’s Disease Assessment Scale Plus

Figure 4.6A describes the predictors of latent variable PA and latent variable sleep latency. Predictors for latent variable PA explained 16% of the variance, with greater age ($\beta = -0.23; p<0.01$) and female sex ($\beta = -2.18; p = 0.02$) associated with lower PA. Predictors for our latent variable of sleep latency explained 14% of the variance with sleep medication use ($\beta = 2.28; p = 0.03$) and average number of awakenings ($\beta = -2.15 p<0.01$). Figure 4.6B describes the relationship between PA and cognitive performance, wherein higher PA was significantly associated with better performance on ADAS-Cog Plus independently of sleep latency ($\beta = -0.02; p<0.01$). Figure 4.6C shows that sleep latency was not significantly associated with ADAS-Cog Plus performance independently of PA. We found that there was no significant relationship between PA and sleep latency (Figure 4.6D).

4.4 Discussion

Our study is the first to examine the independent contributions of PA and sleep quality towards cognitive function. Specifically, we provide evidence that PA is positively associated with older adult cognitive function independently of sleep quality, and sleep efficiency is positively associated with older adult cognitive function independently of PA. Our results align with current evidence indicating the importance of PA and sleep efficiency for maintaining cognitive health [106, 156, 377, 560-562]. However, since we did not find any relationships between PA and any
Figure 4.6 Structural equation models exploring the relationship of physical activity with sleep latency

Significant relationships and standardized estimates ($p < 0.05$; *$p < 0.01$) are displayed. Models have been simplified for clarity. **Path A:** Black dotted lines represent predictors of PA over 14 days. Grey dotted lines represent predictors of sleep efficiency over 14 days. **Path B:** Black solid line represents the relationship of PA with cognitive performance on the Alzheimer’s Disease Assessment Scale Plus (ADAS-Cog Plus); controlling for age, sex, education, and sleep efficiency. **Path C:** Grey solid line represents the relationship of sleep latency with cognitive performance on the ADAS-Cog Plus; controlling for age, sex, education and PA. **Path D:** Outlined double-arrows represent the relationship between PA and sleep latency; standardized-betas and p-values are shown in box.
sleep quality index, we suggest that PA and sleep efficiency are associated with cognitive function through independent mechanisms.

4.4.1 The independent relationships of physical activity and sleep with cognitive function

Our study examined the association of PA with cognitive performance while controlling for different measures of sleep quality. Higher PA was associated with better cognitive performance independently of 1) subjectively-measured sleep quality (i.e., PSQI); and 2) objectively-measured sleep fragmentation, sleep duration, and sleep latency. Consistent with our data and prior studies [106, 156], others have suggested the importance of ≥150 minutes/week of PA for physical and cognitive health [411, 522]. Our results bolster the recommendation that older adults engage in regular PA to optimize cognitive performance.

We found a positive association between sleep efficiency and cognitive performance. A growing body of evidence has demonstrated that better sleep efficiency is associated with better cognitive performance [377, 560-562], while longer sleep duration does not appear to be associated with better cognitive performance—particularly in older adults [560, 561, 563]. Two potential mechanisms have been proposed to explain why sleep efficiency appears to be more important for cognitive health than total sleep time. One explanation suggests reduced sleep drive and greater sleep fragmentation can occur with longer sleep durations [564-566], while the other suggests that greater sleep efficiency increases the likelihood of progressing through sleep stages (i.e., slow-wave sleep) which benefit the prefrontal cortex [567]. Surprisingly, we found a negative relationship between sleep fragmentation and sleep duration. However, we did not perform polysomnography and thus cannot speculate on whether participants with greater sleep efficiency
spent greater amounts of time in slow-wave sleep. Thus, future research will need to determine why sleep efficiency appears to be related to cognitive performance more than sleep duration.

We did not find that any other sleep measure aside from sleep efficiency was associated with cognitive performance (i.e., PSQI, sleep fragmentation, sleep duration and sleep latency). One potential explanation is the ability of PA to mitigate any cognitive detriments related to poor sleep due to the neuroprotective response to regular PA [180]. Recent cross-sectional evidence suggests PA attenuates the negative impact of poor sleep on executive function in older women [568]. Future studies should examine if the neurophysiological benefits of PA prevent poor sleep from impacting cognition.

4.4.2 The relationship of physical activity and sleep

Current epidemiological evidence consistently suggests PA is associated with better sleep quality [11]. However, most of the evidence for a relationship between PA and sleep quality comes from self-report [11, 365]. Our study provides novel information on the relationship between objectively-measured PA and sleep quality—measured using both objective and subjective methods. The results of this study suggest that PA does not appear to be related to older adult sleep quality.

Given the advanced age of our sample, our findings may be explained by age-related attenuation in the relationship of PA with sleep [365]. One potential reason for this apparent functional weakening in the relationship between PA and sleep is that we simply need less sleep as we age because it is a remnant of maturational processes from earlier in life [376]. In addition, there is
some evidence that underlying changes in older adult neurobiology (e.g., neural atrophy, nocturnal hypoxia, neuroendocrine changes, and altered neuromodulation) may reduce the potential to impact sleep quality through strategies such as PA [296]. While our null findings for a relationship between PA and sleep suggest that there is potentially a functional weakening in the relationship between sleep and PA, this hypothesis still requires further investigation.

Our results indicate that both PA and sleep efficiency are associated with cognitive performance, but it remains unclear how PA and sleep efficiency interact to promote cognitive health. However, recent evidence suggests sleep efficiency may mediate the relationship between PA and cognitive function [377]. These results provide further support for the restoration hypothesis, which suggests that energy expenditure (i.e., PA) stimulates a restoration process whereby sleep allows the body and brain to recuperate [364]. While we did not test a mediation effect of PA and sleep efficiency, our results indicate that in addition to a potential mediation effect, it is possible that PA and sleep efficiency are associated with cognitive health through independent mechanisms.

Our findings also support the importance of measuring PA and sleep using both objective and subjective methods—in part because subjective measures of PA and sleep yield different information from objective measures [286, 373]. While the evidence for a relationship between 1) PA and cognition [156]; and 2) sleep and cognition has been consistently found using both objective and subjective methods [569], the relationship between PA and sleep quality has been described primarily using self-report data [11]. Importantly, meta-analytic data suggests PA in the form of exercise training leads to self-reported improvements in overall sleep quality, sleep latency, and sleep medication use [427]. The authors of this meta-analysis also found that exercise
training led to objective improvements in time spent in stage 1 and stage 2 sleep, although only one study measured sleep using objective methods. PA may be related to different aspects of sleep—both how somebody feels about their sleep, and how they are actually sleeping. We thus cannot overstate the importance of using both objective and subjective measures of PA and sleep for future investigations.

4.4.3 Limitations and future research

This study does not account for time of day when participants engaged in PA, which may play an important role in sleep [2]. We also did not account for different types of light exposure at night, however we are unaware of any available technologies which can differentiate between different types of light (e.g., computer or television screen, reading light, or sunlight). Future research is needed to develop methods to categorize different types of light exposure, since night time light exposure can lead to sleep disruptions.

Our strict inclusion criteria for this analysis required that we omit 19 participants from being analyzed. Because structural equation modeling is based on the general linear model, which assumes the data has a normal distribution, including these data would skew the distribution of our data and increase type I error [554].

The precision of our results may have been affected by measurement error from the MW8. Indeed, previous work from our group found that MW8 measures of sleep quality were often not associated (or even inversely associated) with corresponding measures from the PSQI [286]. Although both MW8 and PSQI have evidence of validity against PSG [298, 453], it is plausible that measurement
error in the MW8—which could lead to both overestimation and underestimation of sleep variables—may explain both our previous findings, as well as those we have described in this paper. The agreement of actigraphy with PSG can be low in individuals with poor sleep quality since these people tend to lie in bed motionless, but awake, for long periods of time [570]. We also estimated latent PA using estimates of daily MVPA, and thus cannot account for how LPA might have altered the relationships we found.

All participants were instructed to continuously wear the watch throughout their 14 days of measurement. Based on our non-wear time estimates using the criteria of Hutto and colleagues [529], there were only two instances where participants had consecutive zero counts for greater than 120 minutes during the day. Not recording wear-time of the MW8 may have potentially impacted the precision of our results, although evidence suggests wrist-worn actigraphy has greater wearer compliance because it is more comfortable to wear during routine activities and while sleeping [571].

We used both objective and subjective measures of sleep (i.e., PSQI and MW8) in this study, however we did not measure PA subjectively by questionnaire. While objective measures typically provide more accurate estimates of PA, subjective measures of PA can provide important contextual information about where and how PA occurs [122]. Thus, future research examining the relationships between PA and sleep should therefore include both objective and subjective measures of PA and sleep.
We did not examine whether individual domains of cognitive function were more (or less) associated with PA and sleep. However, the ADAS-Cog Plus is a sensitive measure which can detect underlying changes in cognitive function, beyond traditional measures of global cognitive function such as MMSE and MoCA [530]. Future work should examine whether the independent associations of PA and sleep with cognitive function are domain-dependent. Finally, we have previously reported the relationship between PA and older adult cognitive function is dependent on cognitive status [411]. Briefly, older adults with MCI, a transition stage between healthy cognition and dementia [18], are less active than their healthy cognitive counterparts and may thus not reach a threshold level of PA to elicit a relationship between PA and cognitive function. Although 75 participants within our study showed signs of probable MCI (i.e., MoCA <26/30; [572]), we did not account for cognitive status within our analyses since this was an exploratory analyses and our sample size was modest. Given the relationships we found in the present study, we suggest future work should examine if the relationships we found are altered by differences in cognitive status.

4.4.4 Conclusion

Our results suggest PA is associated with older adult cognitive function independently of a variety of sleep measures. We also found a relationship between sleep efficiency and cognitive function independently of PA. However, our results do not suggest that PA is associated with any measure of older adult sleep quality, and thus PA and sleep efficiency may be associated with cognitive performance through independent mechanisms.
Chapter 5: Not just for joints—the associations of moderate-to-vigorous physical activity and sedentary behaviour with brain cortical thickness

A version of this chapter is currently accepted for publication in *Medicine and Science in Sports and Exercise* as FALCK RS, Hsu CL, Best JR, Li LC, Egbert AR, Liu-Ambrose T. *Not Just for Joints: The Associations of MVPA and SB with Brain Cortical Thickness.*

### 5.1 Introduction

Aging is characterized by multifaceted changes in brain structure and brain function, resulting in age-related changes in cognitive performance related to memory, processing speed, reasoning, and executive functions [27]. Cortical thinning is also a hallmark of the aging process, beginning in as early as middle adulthood and particularly affecting the prefrontal cortex and the medial temporal lobe [573]. However, declining brain health with increasing age is not inevitable since lifestyle modifications can alter the course of brain aging [38].

Cortical thickness is an integral aspect of cognitive health throughout life [551], and better brain health in later life is inextricably linked to the maintenance of cortical thickness as adults age [574]. Older adults with MCI have less cortical thickness than healthy older adults, while older adults with AD have less cortical thickness than older adults with MCI—suggesting that there may be a progression of cortical thinning which occurs as cognitive health worsens [41]. Cortical thinning in the temporal and parietal lobes also predicts conversion from prodromal to mild AD [44], and thinning in vulnerable cortical regions relates to AD symptom severity—even in the earliest stages of the disease [45]. Cortical thinning is also associated with disruption of cortical-white matter networks in people with dementia [575], further suggesting that the preservation of cortical thickness may be integral to healthy brain aging.
Two lifestyle factors associated with better brain and cognitive health are regular MVPA and limited SB [522]. Briefly, MVPA is any bodily movement which incurs ≥3.0 METs, while SB refers to any waking behaviour which incurs ≤1.5 METs and occurs while sitting or lying down. Meeting the current guidelines of ≥150 minutes/week of MVPA reduces the risk of AD by up to 38% [515], and an estimated 18% of all Alzheimer’s disease cases could be prevented by all adults meeting these guidelines [468]. Too much SB can also negatively impact brain health by reducing glycemic control [258], which lead to brain atrophy, white matter hyper intensities and cerebral infarcts [576]. Importantly, it is critical to examine the role of both MVPA and SB concomitantly since low MVPA and high SB are each distinct risk factors for cognitive impairment [522].

MVPA is associated with greater total gray matter volume [577], and reduced age-associated atrophy in the frontal and temporal lobes [167]. This may be especially critical because cortical thinning in the frontal and temporal lobes is linked to cognitive impairment and dementia [45]. Compared with MVPA, there are few studies which have examined the association between SB and neuroimaging outcomes. However, it has been hypothesized that SB may impact brain and cognitive health by either 1) the inverse of MVPA mechanisms which promote brain and cognitive health; or 2) by compromising glycemic control, which can alter cerebral blood flow and potentially lead to cortical atrophy [522]. One study did find that self-reported SB is associated with reduced cortical thickness in the medial temporal lobe [264], however no study has yet examined whether objectively measured SB is associated with cortical thickness, and few studies have examined whether objectively measured MVPA is associated with better brain health. As we have highlighted previously [122], self-reported levels of MVPA and SB are likely biased. Self-
report is vulnerable to recall bias because MVPA participation among older adults is often intermittent, sporadic, or unstructured, which makes recall extremely difficult and might lead to unintentionally over- or under-reporting MVPA and SB. Furthermore, it is currently unclear whether MVPA is associated with cortical thickness independent of SB or vice-versa. Determining whether each of these behaviours are independently associated with cortical thickness could help refine the public health message for healthy brain aging.

To address these knowledge gaps we investigated the independent relationships of objectively measured MVPA and SB with cortical thickness. Based on the current evidence of how MVPA and SB are associated with brain health, we expected greater MVPA to be associated with greater cortical thickness in the temporal and frontal lobes, while SB would be associated with less cortical thickness in the temporal lobe.

5.2 Methods

5.2.1 Study design

This was a cross-sectional secondary analysis of baseline data from Monitor-OA, a six month proof-of-concept RCT examining the efficacy of a technology-enabled counselling intervention for increasing MVPA and reducing SB in adults with knee osteoarthritis [145]. The study occurred between November 1st 2015 and June 1st 2017. The research protocol was approved by the University of British Columbia Behavioural Research Ethics Board (Application number: H14-01762), and was published on ClinicalTrials.gov (NCT02315664). All participants provided written informed consent.
Figure 5.1 describes the study design. At study entry, all participants (N= 61) underwent a baseline evaluation wherein we measured anthropometrics and demographics, observed MVPA and SB for a period of 7 days, and then performed cognitive testing following this observation period. Prior to the start of the intervention, we recruited a sub-sample of 30 participants for our neuroimaging sub-study, wherein all participants underwent MRI scanning.

5.2.2 Participants

Details of our specific inclusion and exclusion criteria can be found elsewhere [145]. Briefly, we recruited individuals who had a physician confirmed diagnosis of knee osteoarthritis, or passed two criteria for early osteoarthritis: 1) aged 50+ years; and 2) had experienced pain or discomfort in or around the knee lasting >28 consecutive or separate days within the last 12 months [578]. We excluded individuals for the following reasons: 1) were diagnosed with inflammatory arthritis, connective tissue diseases, fibromyalgia, or gout; 2) were using disease modifying anti-rheumatic drugs or gout medications; 3) were planning to receive a total knee arthroplasty or had received a knee arthroplasty; 4) had an acute knee injury or received hyaluronate injections or a steroid injection in the last 6 months; 5) did not have an email address or daily access to a personal computer with internet access; 6) had a body mass index (BMI) of >40 kg/m²; 7) had received a steroid injection in the last six months; 8) were using medications that impaired activity tolerance (such as beta-blockers); or 9) had an inappropriate level of risk for increasing their unsupervised PA. Potential participants completed the Physical Activity Readiness Questionnaire (PAR-Q;
Figure 5.1 STROBE diagram

Participant Recruitment

Baseline Evaluation (N=61)

*Anthropometrics and Demographics*

*Moderate-to-Vigorous Physical Activity and Sedentary Behaviour Measurement*
  * Participants wore SenseWear Mini (Body Media, Pittsburgh, PA, USA) for 7 days. Calculated daily average:
    * Moderate-to-Vigorous Physical Activity (≥3.0 METs; minutes/day)
    * Sedentary Behaviour (<1.5 METs; minutes/day)

*Cognitive Testing*
  * Stroop Task
  * NIH List Sorting Task
  * NIH Picture Sequence Memory Task

Neuroimaging Sub-Study (N=30)

*3T MRI scan*

T<sub>1</sub>-weighted structural MRI
  * TR= 7.7 ms
  * TE= 3.5 ms
  * bandwidth=2.26 kHz
  * FA= 8 degrees
  * FoV= 256 mm
  * acquisition matrix= 256 x 200
  * voxel size= 1 mm<sup>3</sup>
  * 8-channel head matrix coil (SENSE factor= 2.4)
[579]). If a potential risk was identified by the PAR-Q, physician confirmation was required to ensure the participant was able to be physically active without the direct supervision of a health professional.

5.2.3 Measures

5.2.3.1 Demographics and anthropometrics
At baseline, we obtained general health history and demographics information by questionnaire. Height and body weight were ascertained using a calibrated stadiometer and an electronic scale, respectively. We used these data to calculate BMI (kg/m²).

5.2.3.2 Moderate-to-vigorous physical activity and sedentary behaviour
We measured MVPA and SB using the SWA, a multi-sensor monitor that is worn on the upper arm over the triceps [143]. The device integrates tri-axial accelerometer data, physiological sensor data and personal demographic information to provide valid and reliable estimates of older adult MVPA and SB [142, 143]. Participants wore the device on the non-dominant arm for 7 days at each assessment. We reduced data to average minutes/day of MVPA (≥3.0 METs) and minutes/day of SB (≤1.5 METs).

5.2.3.3 Magnetic resonance imaging data acquisition and FreeSurfer analyses
MRI data acquisition was conducted at the University of British Columbia MRI Research Centre using a Philips Achieva 3.0 Tesla MRI scanner with an eight-channel sensitivity encoding neurovascular coil (SENSE factor= 2.4). High-resolution T1 images were obtained with the
following parameters: 1) slice thickness of 1 mm³; 2) repetition time of 7.7 ms; 3) echo time of 3.5 ms; 4) bandwidth of 2.26 kHZ; 5) flip angle of 8 degrees; 6) field of view 256 mm; and 7) acquisition matrix size of 256 x 200.

We used the FreeSurfer version 6.0 image analysis suite [72], developed at the Martinos Centre for Biomedical Imaging by the Laboratory for Computational Neuroimaging (http://surfer.nmr.mgh.harvard.edu/), to calculate cortical thickness. FreeSurfer consists of two processing streams, a surface-based stream and a volume-based stream. The surface-based stream constructs models of the white matter/gray matter boundary and the boundary between the gray matter and cerebrospinal fluid (i.e., pial surface) from which cortical thickness is estimated as the shortest distance between the two. Cortical labelling is based on a subject-independent atlas (i.e., the Talairach space) and the subject-specific values. These labels are then morphed onto a common space (cohort mean) to achieve a common point of reference for each subject relative to the clinical population studied. This coordinate system can be subsequently used to examine associations of cortical thickness with variables of interest [73].

We performed our FreeSurfer analyses (for detailed procedure, see Appendix D) using a recent investigation as a guide [580]. Data processing included skull-stripping [581], motion correction [582], Talairach transformation [75], and atlas registration [76]. Following surface reconstruction and segmentation, the resulting output was visually inspected for quality and accuracy by RSF, CLH, and JRB. Automated skull stripping inaccuracies were manually corrected, intensity normalization failures (requiring the addition of white matter control points), incorrect white matter segmentation, automated topological fixer errors, and pial surface inaccuracies. The recon-
all processing stream was then re-run using the *recon-all –qcache* flag to resample the data onto the FreeSurfer *fsaverage* (cohort mean subject) and smooth the images with a 10-mm full-width at half-maximum (FWHM) Gaussian Kernel.

GLM analyses were then performed to assess the independent associations of MVPA and SB with cortical thickness by implementing the mri_glmfit script using 1) *DOSS* (different offset, same slope) as a design matrix; 2) MVPA and SB as independent variables of interest; and 3) age, sex and education as covariates. We then corrected for multiple comparisons using a cluster-wise correction method [583]. Vertex-wise analyses were corrected for multiple comparisons using the *mri_glmfit-sim* toolbox in FreeSurfer, with a cluster forming threshold of 1.3 (i.e., *p* < 0.05) and cluster-wise probability set to *p* < 0.05. P-values were adjusted for both hemispheres in order to correct for the full search space. This was repeated for 10,000 iterations to derive the location of cluster sizes under the null hypothesis. Clusters surviving cluster-wise correction were then superimposed on *fsaverage* inflated surfaces using *tksurfer*, a GUI application available in FreeSurfer.

### 5.3 Results

#### 5.3.1 Participant characteristics

Participant characteristics are described in Table 5.1. There were no significant differences in any descriptive variables between participants included in this sub-study (N= 30) and those from the full sample who were not included (N= 31).
Table 5.1 Participant characteristics—mean (SD) or %

<table>
<thead>
<tr>
<th>Participant Characteristic</th>
<th>All Participants (N= 61)</th>
<th>MRI Participants (N= 30)</th>
<th>Non-MRI Participants (N= 31)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (9)</td>
<td>61 (9)</td>
<td>63 (8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td>50, 81%</td>
<td>24, 80%</td>
<td>26, 84%</td>
<td>0.95</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.20 (5.10)</td>
<td>29.82 (4.85)</td>
<td>28.61 (5.34)</td>
<td>0.36</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High School Degree or Less</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11, 18%</td>
<td>6, 20%</td>
<td>5, 16%</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Some University</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19, 31%</td>
<td>6, 20%</td>
<td>13, 42%</td>
<td></td>
</tr>
<tr>
<td><strong>University Degree or Higher</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31, 51%</td>
<td>18, 60%</td>
<td>13, 42%</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-vigorous Physical Activity (min/day)</td>
<td>85 (74)</td>
<td>70 (48)</td>
<td>99 (91)</td>
<td>0.12</td>
</tr>
<tr>
<td>Sedentary Behaviour (min/day)</td>
<td>693 (138)</td>
<td>698 (118)</td>
<td>688 (157)</td>
<td>0.77</td>
</tr>
<tr>
<td>Total Brain Volume (mm3)</td>
<td>-</td>
<td>1063234 (95729)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total Gray Matter Volume (mm3)</td>
<td>-</td>
<td>589401 (50900)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total Cerebral White Matter Volume (mm3)</td>
<td>-</td>
<td>446701 (48546)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Whole Brain Average Cortical Thickness (mm2)</td>
<td>-</td>
<td>2.43 (0.08)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Note: p-values from independent samples t-tests and chi-square tests for differences between MRI participants and Non-MRI participants.
For participants included, mean participant age was 61 years (SD= 9 years), 80% of the sample was female, and average BMI was 29.82 kg/m\(^2\) (SD= 4.85 kg/m\(^2\)). Participants engaged in 70 minutes/day (SD= 48 minutes/day) and 698 minutes/day (SD= 118 minutes/day) of MVPA and SB, respectively. Average total brain volume was 1,063,234 mm\(^3\) (SD= 95,729 mm\(^3\)), and average cortical thickness was 2.43 mm\(^2\) (SD= 0.08 mm\(^2\)).

5.3.2 Independent relationships of moderate-to-vigorous physical activity and sedentary behaviour with cortical thickness

We identified two significant clusters which survived cluster-wise correction in the left superior frontal gyrus (cluster size= 1,204 mm\(^2\); cortical thickness range: 2.41 – 3.15 mm\(^2\); \(p< 0.05\)) and in the temporal pole (cluster size= 855 mm\(^2\); cortical thickness range: 2.59 – 3.72 mm\(^2\); \(p< 0.05\)), where participants who engaged in greater amounts of MVPA showed greater cortical thickness in these regions independent of time spent in SB (Figure 5.2). No clusters survived correction when examining the relationship between SB and cortical thickness.

5.4 Discussion

Our results suggest that MVPA, but not SB, is associated with greater cortical thickness in the superior frontal gyrus and the temporal pole in community-dwelling older adults. Cortical thinning of the frontal and temporal lobes are each associated with aging and dementia [38, 41, 44, 45, 167, 573, 574], and thus engaging in regular MVPA is integral for maintaining brain health in older adulthood.
Figure 5.2 Significant multiple comparison corrected clusters of greater cortical thickness associated with higher moderate-to-vigorous physical activity independent of sedentary behaviour

Higher moderate-to-vigorous physical activity is associated with greater cortical thickness in the A) temporal pole; and B) superior frontal gyrus of the left hemisphere.
Contrary to our hypothesis, our results do not indicate that greater amounts of SB are associated with less cortical thickness independent of MVPA. Only one study to date has examined the relationship between SB and brain health [264]. The authors found that higher amounts of self-reported SB were associated with decreased medial temporal lobe thickness, however our results do not indicate that SB is associated with brain structure independent of MVPA. One potential explanation is that higher amounts of MVPA provides a neuroprotective response which ameliorates the negative consequences of too much SB. Indeed, our sample was both highly active and highly sedentary, engaging in an average of 70 min/day of MVPA and nearly 12 hours/day of SB. It is thus plausible that the negative cellular consequences of too much SB affects the same pathways by which MVPA improves brain health [522]. While engaging in high amounts of SB appears to have deleterious effects on glucose tolerance, which appears to be critical for maintaining brain health [258, 576], even single bouts of MVPA in the form of exercise can have dramatic effects on glucose tolerance [271]. MVPA in the form of exercise training improves glycemic control, with the most substantial evidence coming from studies of people with type 2 diabetes mellitus [584], who are often more sedentary than their healthy peers [585]. Moreover, MVPA in the form of exercise training in adults with impaired glycemic control improves insulin sensitivity and cognitive function [191], further implicating that high amounts of MVPA may shield the brain from the consequences of high SB on brain health.

While our study appears to further support evidence that high MVPA mollifies some of the negative consequences of SB on brain health, the science is far from settled. Epidemiological data points to high SB being a risk factor for metabolic disease independent of MVPA [258], and there is at least some indication that SB is associated with poorer cognitive health independent of MVPA.
Moreover, there is a growing body of evidence which suggests that higher amounts of LPA (i.e., 1.5-3.0 METs), such as household chores, may also help maintain brain health [168]. Although our exploratory investigation cannot definitively determine which of these behaviours is most critical to promoting better brain health, our results indicate that higher MVPA is critical to maintaining cortical thickness in areas associated with cognitive decline independent of SB [41, 44, 45]. Based on the current results, and keeping with the current guidelines for healthy cognitive aging [522], we recommend that all adults 1) engage in ≥150 minutes/week of MVPA; and 2) limit discretionary SB to <2 hours/day.

5.4.1 Limitations

There are a number of study limitations, most importantly our cross-sectional design such that no causal effects can be elucidated. Our sample was composed of adults with knee osteoarthritis, and thus our results may not generalize to those without knee osteoarthritis. However, osteoarthritis is a common condition in later life with 9% of all men and 18% of all women over 60 years of age have osteoarthritis [586].

Another important limitation is that due to our small sample size we were only powered to detect modest associations between MVPA and SB with brain structure (f²= 0.28). A subsequent examination of whether these residual differences in brain structure are associated with cognitive performance would have required much more robust associations, and thus we could not adequately examine whether brain regions which were associated with MVPA were also associated with cognitive function. Indeed, this is often a limitation of neuroimaging studies, given the high costs of MRI. While we cannot assess whether cortical thinning in the superior frontal
region and the temporal pole are also associated with poorer cognitive performance in this study, we think it important for future studies to have adequate power to not only detect relationships between MVPA and SB with brain structure but also to determine whether differences in brain structure are associated with differences in cognitive performance.

We did not control for intracranial volume (ICV) within our analyses—which is often considered to be an important covariate for volumetric analyses of the brain and brain regions [587]. However, we chose not to control for ICV in our analyses because we were uninterested in group differences—such as between healthy older adults and those with neurodegenerative disease. For example, if our study had examined differences in MVPA and SB of older adults with and without cognitive impairment, it would make sense to control for ICV since older adults with cognitive impairment probably have different ICVs from their healthy cognitive counterparts. In our analyses, we did control for age, sex, and education; each of these variables is correlated with brain structure [38, 573]. Hence, our statistical model is a parsimonious approach to understanding how MVPA and SB are associated with brain structure.

Our sample was also highly active in comparison to the general population. Less than 95% of adults meet the current MVPA guidelines of 150 minutes/week of activity [96], however most of our sample well exceeded these guidelines. One potential explanation, is that this study was conducted in the Greater Vancouver Area of British Columbia, Canada. More than 60% of adults living in British Columbia are classified as active (i.e., meeting current MVPA guidelines) according the British Columbia Ministry of Health [588], and adults living in British Columbia are the most active in all of Canada. Our results should thus be confirmed in less active populations.
While the SWA provides valid and reliable estimates of MVPA [142, 143], there are potential issues with the device’s estimates of SB. Specifically, SB is defined as any waking behaviour which incurs less than 1.5 METs and is performed from the seated or lying position [522]; the SWA cannot detect body position and thus our estimates of SB may be inaccurate. However, it is important to note that there is no one best method for measuring SB. Multimodal sensors such as the SWA can accurately estimate energy expenditure, but cannot detect posture; inclinometers (e.g., activPAL) can index posture, but provide less accurate estimates of energy expenditure. Future studies should thus consider measurement protocols wherein measures of energy expenditure are combined with measures of body position.

Lastly, we did not measure cardiovascular fitness, and thus cannot determine whether fitness or MVPA and SB levels are more important for older adult brain health. Investigations into how MVPA and SB are associated with brain health have traditionally used cardiovascular fitness as a proxy or endpoint of activity level [577]. While these studies have consistently found an association between cardiovascular fitness and better brain structure, there is debate about whether cardiovascular fitness is directly linked to MVPA level [589]. Future research is thus needed to determine whether fitness or activity level is more important for brain health.

5.4.2 Conclusion

In summary, higher MVPA is associated with greater cortical thickness in the superior frontal gyrus and the temporal pole, independent of SB level. Our results help refine the current healthy cognitive aging guidelines on MVPA and SB by indicating that MVPA maintains cortical structure
in later life independent of SB level [522]. Encouraging all adults to meet MVPA guidelines may therefore help maintain the brain health of the population. Future research should examine how MVPA level, independent of cardiovascular fitness, is associated with cortical thickness.
Chapter 6: Can we improve cognitive function among adults with osteoarthritis by increasing moderate-to-vigorous physical activity and reducing sedentary behaviour?

Secondary analysis of the MONITOR-OA study


6.1 Introduction

One new diagnosis of osteoarthritis occurs every 60 seconds, such that 9.6% of all men and 18.0% of all women over age 60 have symptomatic osteoarthritis [590, 591]. Of those living with osteoarthritis, 80% will have limitations in movement and 25% cannot perform their major daily activities of life [591]. The pain of osteoarthritis is associated with 1) reduced physical function and mobility [592]; and 2) increased frailty and falls risk [593]. While total knee replacement is effective for end-stage osteoarthritis [594], it does not uniformly restore joint function, and 20% of patients continue to experience pain [595].

Preliminary evidence also suggests osteoarthritis is associated with an increased risk of cognitive decline and dementia [596]. Although the association between osteoarthritis and dementia is still under investigation [597], animal models suggest that peripheral inflammation associated with osteoarthritis may trigger neural inflammation and induce AD pathology—the most common form of dementia [598]. Given that the number of cases of osteoarthritis and dementia are each increasing as the population of older adults continues to grow [1, 586], there is an urgent need for
effective treatment strategies for osteoarthritis symptoms since this may also help reduce dementia prevalence.

Two frontline strategies for improving osteoarthritis symptoms are increasing MVPA and reducing SB [599-603]. Briefly, MVPA refers to any behaviour which incurs ≥3.0 METs, while SB refers to any behaviour which incurs ≤1.5 METs and occurs while sitting or lying down. While osteoarthritis is linked to declines in joint protective biomarkers such as lubricin and pituitary adenylate cyclase-activating polypeptide (PACAP), and increases in inflammatory markers and apoptotic signaling [604, 605], animal models of osteoarthritis indicate that MVPA can 1) promote lubricin synthesis [606-608]; 2) down-regulate apoptotic signalling [607]; 3) down-regulate inflammatory markers of osteoarthritis including interleukin-1 [608]; and 4) may stimulate the production of PACAP [609]. Increased MVPA can also improve strength and balance in adults with arthritis [610], reduce the risk of falls [611], and reduce osteoarthritis symptoms such as pain, fatigue, and joint stiffness [612]. While less is known about how SB may impact the symptoms of osteoarthritis, epidemiological evidence suggests that reduced SB is associated with better physical function in adults with osteoarthritis — independent of MVPA time [599, 600].

There is also evidence that both high MVPA and low SB are neuroprotective [156, 522]. Animal models suggest that MVPA reduces pro-inflammatory markers and Aβ protein levels in transgenic mice predisposed to AD [239], and human epidemiological data consistently indicates that MVPA is associated with better cognitive function and a lower risk of cognitive decline [156]. Greater amounts of SB may negatively impact the cellular mechanisms by which MVPA improves cognitive health [6], and may alter the connectivity of the brain such that cognitive function
worsens with greater SB [7]. As such, current guidelines suggest that all adults should engage in ≥150 minutes of MVPA each week and limit discretionary SB as much as possible [522].

Given that 1) increasing MVPA and reducing SB promotes cellular mechanisms which reduce osteoarthritis associated inflammatory and apoptotic responses [6, 239, 606-609]; and 2) osteoarthritis associated inflammation and apoptotic signalling increases dementia risk [598], it is plausible that increasing MVPA and reducing SB is an effective frontline dementia prevention strategy for adults with osteoarthritis. Unfortunately, the uptake of knowledge about the importance of MVPA and SB for controlling osteoarthritis symptoms and reducing dementia risk has been slow. Among adults living with osteoarthritis, 87% do not meet current recommendations of ≥150 minutes/week of MVPA [613], and people with osteoarthritis spend 61% of all waking hours in SB [614]. Finding strategies to address this knowledge-to-action gap are thus greatly needed since increasing MVPA and reducing SB among adults with osteoarthritis may provide benefits for both physical and cognitive health.

One promising strategy for increasing MVPA and/or reducing SB is consumer-available, wearable activity-monitoring technology. These devices present several distinct advantages as a MVPA promotion and SB reduction tool including: 1) adults typically perceive activity-monitors as useful [409]; 2) these devices incorporate multiple behavioural change strategies [410]; and 3) clinicians can readily use these devices to help promote behaviour change among their underactive patients [411]. Importantly, we recently determined that a wearable technology enabled counselling program for adults with knee osteoarthritis increased MVPA by 25 minutes/day and improved osteoarthritis symptoms [145]. Within this study, we included secondary measures to determine if
increasing MVPA and/or reducing SB among adults with knee osteoarthritis could also benefit cognitive function. Thus, the aim of the present paper is to determine whether this intervention to increase MVPA and reduce SB among adults with osteoarthritis also improved cognitive function.

6.2 Methods

6.2.1 Study design

This study was a secondary analysis of Monitor-OA, a six month RCT examining the efficacy of a technology-enabled counselling intervention for increasing MVPA and reducing SB in people with knee osteoarthritis [145]. The study occurred between November 1st 2015 and June 1st 2017. We used a randomized delayed-control design. In this study design, randomization determined the timing of when the intervention was provided (i.e., immediately vs. a 2-month delay).

6.2.2 Participants

We recruited community-dwelling adults from Vancouver, British Columbia who had a physician confirmed diagnosis of knee osteoarthritis, or passed two criteria for early osteoarthritis: 1) aged 50+ years; and 2) experienced knee pain during the previous year lasting >28 separate or consecutive days [578]. Participants were excluded if they 1) had been diagnosed with inflammatory arthritis, connective tissue diseases, fibromyalgia, or gout; 2) used anti-rheumatic drugs or gout medications; 3) had previously underwent knee arthroplasty, or were on the waitlist to receive total knee arthroplasty; 4) had suffered an acute knee injury in the past six months; 5) had a BMI of >40 kg/m²; 6) had received a steroid injection or a hyaluronate injection in the last 6 months; 7) were using medications which impaired PA tolerance (e.g., beta blockers), or had an
inappropriate level of risk for increasing their PA. Participants were also excluded if they did not have access to a computer in their home, or did not have a personal email address. Potential participants completed the PAR-Q [579]. If a potential risk was identified by the PAR-Q, physician confirmation was required to ensure the participant was able to be physically active without supervision of a health professional.

The CONSORT (Consolidated Standards of Reporting Trials) flowchart in Figure 6.1 shows the number of participants in the treatment arms at each stage of the study [615]. The research protocol was approved by the University of British Columbia Behavioural Research Ethics Board (Application number: H14-01762), and was published in ClinicalTrials.gov (NCT02315664).

6.2.3 Measures

Trained staff members administered all testing procedures. We assessed participants at baseline, 2 months, 4 months, and 6 months follow-up. In this paper we report data from baseline, 2 months, and 4 months.

6.2.3.1 Demographics

At baseline, we obtained general health history and demographics information by questionnaire. Height and weight were ascertained using a calibrated stadiometer and an electronic scale, respectively. This information was used to determine BMI. In addition, we assessed global cognitive function at baseline using the MMSE and the MoCA [457, 487].
Figure 6.1 CONSORT diagram

Interested (n=278)  
Assessed eligibility (n=217)  
Consented (n=64)  
Baseline Completed (n=61)  
Withdrawn (n=3)  
Randomized

Immediate Intervention (n=30)  
Completed Assessment (n=28)  
Withdrawn (n=1)  
Refused future cognitive assessments (n=1)

Delayed Intervention (n=31)  
Completed Assessment (n=26)  
Withdrawn (n=3)  
Refused future cognitive assessments (n=1)  
Skipped Assessment (n=1)

2 Month Follow-up  
4 Month Follow-up  
6 Month Follow-up  
Completed Assessment (n=25)  
Withdrawn (n=1)  
Skipped Assessment (n=2)

Completed Assessment (n=26)  
Skipped Assessment (n=1)
6.2.3.2 Moderate-to-vigorous physical activity and sedentary behaviour

We measured MVPA and SB using the SWA, a multi-sensor monitor worn on the upper arm over the triceps [138]. Briefly, the device integrates tri-axial accelerometer data, physiological sensor data and personal demographic information to provide valid and reliable estimates of MVPA and SB [138, 140-143]. Participants wore the device on the non-dominant arm for 7 days at each assessment. For our analyses, we examined time spent in MVPA in periods of 10 or more minutes, and time spent in SB in periods of 20 or more minutes.

6.2.3.3 Cognitive function

We measured cognitive function using the NIHTB-CB [461]. Briefly, the NIHTB-CB provides a brief, convenient set of computerized and standardized measures of cognitive function. We examined two specific cognitive subdomains: 1) episodic memory using the picture sequence memory task [462]; and 2) working memory using the list-sorting task [463]. Empirical evidence suggests increasing MVPA or reducing SB can influence each of these domains of cognitive function [102, 522]. Briefly, the picture sequence memory task assesses episodic memory by having participants remember a sequence of actions embedded within a story. Participants re-arrange several pictures on the computer to match the sequence of events in the story. The list-sorting task assesses working memory by asking participants to repeat the names of orally—and visually—presented stimuli in order of size, from smallest largest. The number of items per set increases from one trial to the next and is discontinued once 2 trials of the same length are failed. Three trials of increasing length are completed. We recorded age-corrected scores for each measure.
6.2.4 Randomization

After completing the baseline assessment, eligible participants were randomly assigned to the Immediate Intervention (I-INT) or the Delayed Intervention (i.e. control; D-INT) in a 1:1 allocation ratio. Randomization was performed using computer-generated random numbers in variable block sizes. The D-INT received the same intervention as the I-INT after a 2-month wait.

6.2.5 Intervention

Details of the intervention have been described previously [145]. Briefly, the intervention consisted of participants attending a 1.5-hour session, where they received: 1) a standardized group education session about the benefits of increasing MVPA and reducing SB; 2) a Fitbit® Flex™; and 3) individual activity counselling with a physiotherapist. The education session was delivered in groups of 2–3 participants. The individual activity counselling session followed the BAP approach [402]. The physiotherapist guided participants to identify their MVPA goals (e.g., begin RT, start cycling, join a walking group, etc.), develop an action plan (i.e., where they plan to perform their MVPA goal, how often, and for how long), identify barriers and solutions, and then rate their confidence in executing the plan. For SB, the physiotherapists began by asking participants to estimate their sitting time in a normal day. Participants were then asked to identify ways to break up their sitting time into shorter bouts.

Following the education session, participants were provided with a Fitbit Flex™ which they were instructed to wear 24 hours/day except during water-based activity (i.e., swimming or bathing) or when charging the device. The Fitbit data were wirelessly synchronized with Fitbit’s online Dashboard which could be viewed only by the participants and the study physiotherapist. During
the intervention period, the physiotherapist reviewed the individual’s MVPA on the Dashboard and progressively modified the activity goals during 4 biweekly phone calls. During these phone calls, we also monitored participant adherence to SB goals using self-report. Specifically, participants were asked at each biweekly phone call whether they fully met, partially met, or did not meet their SB goal. These goals were then modified as needed.

6.2.6 Statistical analyses

We conducted all statistical analyses using R version 3.3.1 in the *lsmeans* 2.26-3, *lmerTest* 2.0-33, and *mice* 2.46.0 packages. Descriptive statistics were used to summarize participant demographics. In order to account for missing data at each follow-up time point, we performed multiple imputation in the *mice* 2.46.0 package using predicted mean matching (5 imputations; 20 iterations each), and visually checked for convergence. All statistical models used pooled estimates from all 5 imputed data sets. Plots and graphs were created using *ggplot2* 2.2.1. Our statistical code can be found in Appendix D.

6.2.6.1 Main analyses

We evaluated between-group differences (I-INT vs. D-INT) on the outcomes of interest following the primary intervention (i.e., Baseline – 2 Months) using the intention-to-treat principle, as per our primary outcomes paper [145]. Two separate analyses of covariance (ANCOVA) models were conducted, wherein cognitive performance at 2 months was the dependent variable and treatment group was the independent variable of interest; both models controlled for baseline cognitive performance. We estimated group mean changes in cognitive function and corresponding 95%
confidence intervals pooled across the 5 imputed datasets, as well as estimated group mean difference (with 95% CI) and estimated Cohen’s $d$ effect size.

### 6.2.6.2 Secondary analyses

We also examined whether changes in MVPA or SB during the intervention were associated with changes in cognitive function. We created change scores (i.e., I-INT= Baseline – 2 Months; D-INT= Baseline – 4 Months) for MVPA, SB, the list-sorting task, and the picture sequence memory task. We performed four separate multiple linear regression models wherein changes in cognitive performance (i.e., list-sorting memory or picture sequence memory) during the intervention were specified as the dependent variable, and changes in MVPA (or SB) was specified as the independent variable of interest. Each model included 1) baseline score for the cognitive performance variable of interest; 2) baseline MVPA (or SB); and 3) treatment group as covariates of no interest. We report unstandardized beta values and standard errors. Given our sample size, and a two-tailed $\alpha= 0.05$, we had 80% power to detect a two-sided correlation with a medium effect size of $|\rho|= 0.34$ [557].

### 6.3 Results

#### 6.3.1 Participant characteristics

From 2015–2016, 278 people indicated an interest to participate, and 64 met the eligibility criteria (Figure 6.1). Of those, we recruited 61 participants (I-INT: N=30; D-INT: N=31). As described in Table 6.1, both groups had similar age (I-INT: 61.73 [SD 9.40] years; D-INT: 62.61 [8.54]), BMI (I-INT: 29.16 [5.46] kg/m$^2$; D-INT: 29.24 [4.82], and time spent in MVPA (I-INT: 83.44 [60.80]
minutes/day; D-INT: 86.19 [86.19] minutes/day) and SB (I-INT: 681.96 [111.51] minutes/day; D-INT: 703.05 [161.17] minutes/day) at baseline. Participants in I-INT had a lower picture sequence memory score (I-INT: 102.04 [17.22]; D-INT: 112.53 [14.67]), but there were similar list-sorting scores at baseline for both groups (I-INT: 102.05 [17.22]; D-INT: 102.42 [14.64]).

Table 6.1 Baseline characteristics

<table>
<thead>
<tr>
<th>Participant Characteristic</th>
<th>Immediate Intervention (N= 30)</th>
<th>Delayed Intervention (N= 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.73 (9.40)</td>
<td>62.61 (8.54)</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td>22, 73%</td>
<td>28, 90%</td>
</tr>
<tr>
<td>Education (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>5, 17%</td>
<td>6, 19%</td>
</tr>
<tr>
<td>Some university</td>
<td>10, 33%</td>
<td>9, 29%</td>
</tr>
<tr>
<td>University degree or higher</td>
<td>15, 50%</td>
<td>16, 52%</td>
</tr>
<tr>
<td>Body Mass Index (kg/m)</td>
<td>29.16 (5.46)</td>
<td>29.24 (4.82)</td>
</tr>
<tr>
<td>Moderate-to-Vigorous Physical Activity (min/day)</td>
<td>83.44 (60.80)</td>
<td>86.19 (86.19)</td>
</tr>
<tr>
<td>Sedentary Behaviour (min/day)</td>
<td>681.96 (111.51)</td>
<td>703.05 (161.17)</td>
</tr>
<tr>
<td>Mini-Mental State Exam</td>
<td>28.03 (2.62)</td>
<td>28.62 (1.35)</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>27.27 (2.53)</td>
<td>26.24 (2.86)</td>
</tr>
<tr>
<td>List-Sorting Task</td>
<td>102.05 (13.03)</td>
<td>102.42 (14.64)</td>
</tr>
<tr>
<td>Picture Sequence Memory Task</td>
<td>102.04 (17.22)</td>
<td>112.53 (14.67)</td>
</tr>
</tbody>
</table>

6.3.2 Changes in cognitive function

Group differences in cognitive performance—accounting for baseline cognitive performance—are illustrated in Figure 6.2. Briefly, there were no statistically significant differences between groups following the intervention. As described in Table 6.2, we calculated a small improvement of the I-INT compared to D-INT for picture sequence memory (estimated mean difference: 1.27; 95% CI [-9.27, 11.81]; d= 0.10), and a small improvement of the D-INT compared to the I-INT for list-sorting memory (estimated mean difference: -1.64; 95% CI [-8.72, 5.44]; d= -0.19).
Figure 6.2 Changes in cognitive performance by treatment group (Baseline – 2 Months)

A) Change in NIH Toolbox List Sorting Task (i.e., Working Memory) score by treatment group adjusting for baseline cognitive score.
B) Change in NIH Toolbox Picture Sequence Memory Task (i.e., Episodic Memory) score by treatment group adjusting for baseline cognitive score.
Table 6.2 Changes in cognitive function (Baseline – 2 Months) by treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate Intervention Group Mean [95% CI]</th>
<th>Delayed Intervention Group Mean [95% CI]</th>
<th>Estimated Mean Group Difference [95% CI]</th>
<th>$d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>List Sorting Task</td>
<td>2.90 [-1.55, 7.35]</td>
<td>4.53 [-0.53, 9.59]</td>
<td>-1.64 [-8.72, 5.44]</td>
<td>-0.19</td>
</tr>
<tr>
<td>Picture Sequence Memory Task</td>
<td>4.21 [-2.55, 10.97]</td>
<td>2.95 [-6.36, 12.26]</td>
<td>1.27 [-9.27, 11.81]</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Note: All estimates adjusted for cognitive score at baseline
6.3.3 Correlation between moderate-to-vigorous physical activity and sedentary behaviour changes with changes in cognitive function

The relationship between changes in MVPA and changes in cognitive function are illustrated in Figure 6.3. There were no statistically significant relationships between changes in MVPA and changes in cognitive function. Increases in MVPA were correlated with changes in list-sorting memory in the expected direction (B= 0.04; 95% CI [-0.07, 0.14]), however changes in picture sequence memory appeared to be negatively correlated with increases in MVPA (B= -0.02; 95% CI [-0.15, 0.12]).

The relationship between changes in SB and changes in cognitive function are illustrated in Figure 6.4. There were no statistically significant relationships between changes in SB and changes in either picture sequence memory (B= -0.01; 95% CI [-0.09, 0.07]) or list-sorting memory (B= 0.00; 95% CI [-0.09, 0.10]).

6.4 Discussion

Although we previously determined this intervention can increase MVPA and improve quality of life among adults with knee osteoarthritis [145], there does not appear to be sufficient evidence that our intervention can also improve cognitive function within this population. However, our results suggest that future research on the role of MVPA and SB for maintaining cognitive health among adults with osteoarthritis is warranted. Given that most adults with osteoarthritis are inactive [614], and thus more at risk to future cognitive decline [156, 522], we believe that such research would be valuable. We now discuss potential explanations for our findings.
Figure 6.3 Relationship between intervention associated changes (i.e., Immediate Intervention= Baseline – 2 Months; Delayed Intervention= Baseline – 4 Months) in moderate-to-vigorous physical activity (minutes/day) and changes in cognitive function.

Each model includes 1) baseline score for the cognitive performance variable of interest; 2) baseline moderate-to-vigorous physical activity; and 3) treatment group as covariates of no interest.
Figure 6.4 Relationship between intervention associated changes (i.e., Immediate Intervention = Baseline – 2 Months; Delayed Intervention = Baseline – 4 Months) in sedentary behaviour (minutes/day) and changes in cognitive function.

Each model includes 1) baseline score for the cognitive performance variable of interest; 2) baseline sedentary behaviour; and 3) treatment group as covariates of no interest.
While there is evidence that MVPA in the form of exercise training can improve cognitive function [154], the results of community-based MVPA interventions to promote cognitive health have been far less conclusive [616]. Importantly, the effects of MVPA on cognitive function seem to be largest for individuals who are underactive, while regular MVPA may be mainly neuroprotective for individuals who are meeting current guidelines [617]. Our participants were already highly active at baseline, and thus changes in MVPA may have had limited impact on cognitive function due to high basal levels. Moreover, the high activity level of our sample at baseline suggests that the results may not be generalizable to most adults with osteoarthritis—who are sedentary. In order to first determine the efficacy of MVPA as a treatment for maintaining cognitive health for adults with osteoarthritis, future trials should therefore recruit less active individuals since they 1) are more generalizable to the osteoarthritis population; and 2) will more likely reap the most benefits from increasing their MVPA.

To date, most of the evidence examining how SB impacts cognitive health comes from epidemiological data [6, 7, 522]. Our study is the first to examine if an intervention to reduce SB can improve cognitive health among adults with osteoarthritis. The results do not appear to suggest reductions in SB are associated with improvements in cognitive function; however, our intervention did not significantly reduce time spent in SB [145]. Preliminary evidence does suggest reductions in sedentary time may reverse the deleterious physiological effects of SB—such as impaired glucose and lipid metabolism [88]. Healthy glucose and lipid metabolism are linked to better cognitive health [263]. Thus, while our results cannot determine whether reducing SB can improve cognitive function, there does appear to be a plausible mechanism by which reduced SB may benefit cognitive function.
This was a secondary analysis of a proof-of-concept RCT, and thus we think the logical next step is for an adequately powered RCT to determine the efficacy of this intervention to promote cognitive health among adults with osteoarthritis. A recent meta-analysis suggests that MVPA in the form of exercise training has a modest effect size on cognitive function of $d=0.29$ [154]. Based on this effect size, we post-hoc investigated the necessary sample size to perform an adequately powered RCT to determine the efficacy of this intervention to promote cognitive health among adults with osteoarthritis. A recent meta-analysis suggests that MVPA in the form of exercise training has a modest effect size on cognitive function of $d=0.29$ [154]. Based on this effect size, we post-hoc investigated the necessary sample size to perform an adequately powered RCT to improve cognitive function using G*Power 3.1 [557]. In order to detect an effect size of the magnitude suggested by Northey and colleagues [154], we would need at least 376 participants to achieve 80% power (assuming a two-sided $\alpha=0.05$). The study we report herein was thus under-powered, however we would expect the effect sizes for this intervention to increase through two simple strategies. First, future studies should exclude adults that are already physically active since the largest effects of MVPA on health occur for individuals who are inactive [90, 439]. Second, increasing the length of time between assessment points would help reduce the potential for practice effects to occur on cognitive tests [618], and provide adequate time for eliciting changes in cognitive function which evidence suggests are larger after at least 6 months of increased MVPA [102].

6.4.1 Clinical applications

Although we did not find that our intervention significantly improved cognitive function, there are several potential clinical applications to our study. First, we previously demonstrated that clinicians (i.e., physical therapists) can use consumer-available wearable activity-monitors such as a Fitbit to promote MVPA and reduce SB among their patients with osteoarthritis [145]. Given the health care system has an untapped capacity for promoting changes in MVPA and SB, which to
date has not been fully developed [527], a first step towards harnessing this potential to promote behaviour change is for clinicians to track their patients’ MVPA and SB using wearable activity-monitors. At minimum, clinicians should query about activity during their consultations with osteoarthritis patients [543].

Secondly, both osteoarthritis and SB may increase the risk of cognitive impairment and dementia [156, 522, 596-598]. In contrast, engagement in MVPA reduces dementia risk and promotes overall cognitive and physical health [156, 239, 601-603]. Adults with osteoarthritis should therefore be encouraged to adhere to the current public health recommendations of engaging in ≥150 minutes/week of MVPA and limiting their SB as much as possible [522]. Importantly, 87% of adults with osteoarthritis are underactive [613], and adults with osteoarthritis spend an average of 61% of the day in SB [614]. MVPA promotion and SB reduction may thus be particularly important for physical and cognitive health in adults with osteoarthritis.

### 6.4.2 Limitations and future research

This was a secondary outcomes analysis, and thus our findings are a preliminary investigation of whether increasing MVPA and reducing SB can improve cognitive function in adults with osteoarthritis. While the SWA provides valid and reliable estimates of energy expenditure for both younger and older adults [138, 619], which can be used to derive time spent in MVPA and time spent in SB, we cannot determine whether time estimated as SB was actually spent sitting or lying down. Hence, future studies to examine changes in SB should use measures of body posture such as the activPAL [620], which can accurately determine whether a person is sitting, standing, or walking.
We did not collect information on medication use, however our participants were community-dwelling adults who were healthy enough to start a physical activity program at study entry. We also did not exclude participants based on current activity level and hence the results may not be generalizable to most people with osteoarthritis—who are often sedentary. Given the high activity level of our participants, the effects of increased MVPA and reduced SB on cognitive function may have been attenuated. We therefore suggest future studies should recruit underactive adults with osteoarthritis, since these individuals are likely to benefit from increased MVPA and reduced SB.

There is growing evidence that the effects of MVPA (and potentially SB) are moderated by age and sex [90, 187], however due to our small sample size, it was not feasible for us to control for age and sex within our analyses. As detailed previously [145], our intervention did not reduce SB which is perhaps due to several shortcomings of the counselling program, which we have rectified. Specifically, the intervention now includes a new SB counselling strategy, and a Fitbit-compatible web app with enhances functionality for setting goals and rewarding behaviours that break up prolonged sitting [621]. This paradigm is currently being tested in a RCT (ClinicalTrial.gov identifier: NCT02554474) involving people with rheumatoid arthritis and systematic lupus erythematosus [622].

6.4.3 Conclusion

While evidence indicates that increasing MVPA and reducing SB can positively impact osteoarthritis symptoms, it is not yet clear whether increasing MVPA and reducing SB can also
promote cognitive health among this population. However, increasing MVPA and reducing SB among adults with osteoarthritis should be a public health priority since it can help maintain physical health and reduce the risk of cognitive impairment and dementia. Clinicians should therefore take the time to counsel their patients with osteoarthritis to engage in \( \geq 150 \) minutes/week of MVPA and limit their SB in order to promote physical and cognitive health.
Chapter 7: Effect of multimodal personalized chronotherapy on sleep and cognitive function in older adults with probable Mild Cognitive Impairment and poor sleep: a randomized clinical trial

A version of this chapter is under review in SLEEP as FALCK RS, Davis JC, Best JR, Chan PCY, Li LC, Wyrough AB, Bennet KJ, Backhouse D, Liu-Ambrose T. Effect of multimodal chronotherapy on sleep quality in older adults with probable Mild Cognitive Impairment and poor sleep: a randomized clinical trial.

7.1 Introduction

Older adults with MCI develop dementia at a rate of 10-30% annually [19], whereas those without MCI develop dementia at a rate of only 1-2% annually [18]. Dysregulated sleep-wake cycles are associated with increased risk of progression from MCI to dementia [346]. Thus, strategies that improve sleep quality among older adult with MCI may minimize their rate of cognitive decline and progression to dementia.

Poor sleep is closely tied to the function of circadian rhythms [2], the ~24-hour biological clock which helps coordinate physiology and behaviour with the solar light-dark cycle [288]. The endogenous human biological clock is synchronized with the solar light-dark cycle through external stimuli (i.e., zeitgebers) by a process known as entrainment [291]. Circadian alignment is critical for good quality sleep and MCI is associated with circadian dysregulation [2, 623].

Chronotherapy is an evidenced-based approach for improving circadian regulation, which uses effectively-timed zeitgebers to strengthen the entrainment of the biological clock to the solar light-dark cycle [2, 430]. BLT uses effectively-timed light, the principle entraining zeitgeber of the
human biological clock, to re-align the biological clock and promote better sleep [291, 434]. PA can also have entraining effects on the biological clock [624], although evidence suggests regular PA—regardless of timing—is associated with better sleep [365]. BLT may also complement and help further promote PA by improving mood and increasing energy levels [625]. A preliminary meta-analysis of 3 studies suggests combining BLT with PA promotion and sleep hygiene education can significantly improve actigraphy-measured sleep quality in older adults with cognitive impairment [448]. Quasi-experimental data also supports the efficacy of using BLT and PA, in conjunction with sleep hygiene education, to improve subjective sleep quality among older adults with insomnia [626]. It is thus plausible that multimodal chronotherapy may be an effective approach to improving the sleep of older adults with MCI and poor sleep. In turn, improvements in sleep from multimodal chronotherapy might also improve cognitive performance among older adults with MCI.

This study investigated whether a multimodal chronotherapy program of individually-timed BLT, health coaching to promote PA, and general sleep hygiene education would improve sleep quality and cognitive function among older adults with probable MCI and poor sleep.

7.2 Methods

7.2.1 Study design and setting

This was a parallel, single-blinded, proof-of-concept RCT (NCT02926157) conducted in the Greater Vancouver area of British Columbia, Canada. The protocol for this study is published elsewhere [449]. Ethical approval was obtained from the University of British Columbia’s Clinical
Research Ethics Board (H16-01029) and the Vancouver Coastal Health Research Institute (V16-01029). All participants provided written informed consent. Figure 7.1 describes the CONSORT flow chart.

7.2.2 Recruitment

Participants were recruited from the community using advertisements placed in local community centers, newspapers, and word-of-mouth referrals. Recruitment and enrollment occurred over 17 months (November 21, 2016 to April 18, 2018). Interested participants were initially screened by telephone; those who remained eligible were invited to an in-person screening. Participants who met our full eligibility criteria were scheduled for baseline assessment.

7.2.3 Inclusion criteria

Eligible participants were community-dwelling men and women: 1) aged 65-85 years; 2) living independently in their own homes; 3) scored >24/30 on the MMSE [487]; 4) scored <26/30 on the MoCA [457]; the MoCA cut-off score correctly identified 90% of a large sample of MCI individuals [572]; 5) had poor subjective sleep quality indicated by a score >5/21 on the PSQI [299]; 6) scored <5/15 on the 15-item Geriatric Depression Scale [627]; 7) in sufficient health to participate in regular PA as indicated by the PAR-Q+ [628]; and 8) able to understand, speak, and read English.
Figure 7.1 CONSORT diagram

Excluded (N= 119)
- Eligible but uninterested (N= 20)
- Did not meet inclusion criteria (N= 99)

Contacted and screened in person (N= 218)

Consented, completed baseline assessment, and randomized (N= 98)

Allocated to INT (N= 48)
- General sleep hygiene classes (Weeks 1 to 4)
- Individually-timed BLT and individually-tailored PA promotion (Weeks 5 to 24)

Completed Assessment (N= 42)

Included in ITT analysis (N= 48)

Excluded (N= 235)
- Eligible but uninterested (N= 45)
- Did not meet inclusion criteria (N= 175)
- Unable to contact (N= 15)

Allocated to INT (N= 48)
- Optional health education classes (Weeks 1 to 4)
- Usual Care (Weeks 5 to 24)

Completed Assessment (N= 46)

Included in ITT analysis (N= 48)

Withdraw after baseline assessment (N= 2)

12 weeks follow-up

Excluded (N= 6)
- Withdrew (N= 5)
- Missed assessment (N= 1)

Completed Assessment (N= 43)

24 weeks follow-up

Excluded (N= 3)
- Withdrew (N= 3)

BLT – Bright Light Therapy; CON – Usual care plus optional education; ITT – Intention-to-treat analysis; INT – Personalized Chronotherapy Intervention; PA – Physical Activity
7.2.4 Exclusion criteria

Individuals were excluded if: 1) diagnosed with dementia of any type; 2) diagnosed with any progressive neurodegenerative disease (e.g., Parkinson’s disease); 3) diagnosed with OSA; 4) receiving continuous positive air pressure (CPAP) treatment; 5) were at high risk for cardiac complications during PA; 6) had clinically important peripheral neuropathy that impacted mobility; or 7) severe musculoskeletal and/or joint disease which impaired mobility.

7.2.5 Randomization and blinding

To ensure concealment of treatment allocation, randomization sequences were generated (www.randomization.com) and held remotely in a secured server accessed only by research staff not involved in the study. To ensure balance over time, permuted blocks of varying size were used. Participants were randomly assigned (1:1) to either multimodal chronotherapy (INT) or an education control (CON). Research personnel performing outcome assessments and data analyses were blinded to group allocation.

7.2.6 Interventions

7.2.6.1 Multimodal chronotherapy (INT)

The INT included four sleep hygiene classes delivered in weeks 1-4, followed by 20 weeks of individually-timed BLT based on each participant's estimated chronotype and sleep profile, and health coaching to promote PA.
Sleep hygiene classes (1x/week; 2 hours/session) provided strategies to protect sleep including the importance of individually-timed BLT and regular PA. Following completion of the 4-week sleep hygiene education course, INT participants met with a trained research assistant to develop an individually-timed BLT schedule. Figure 7.2 describes the individually-timed BLT prescription plan.

The INT participants worked with the research assistant to determine the best regularly scheduled bed time and wake time in order to dedicate 8 hours to sleeping each night (i.e., the sleep window). Results of baseline actigraphy recordings were used to determine the participant’s current sleep window in comparison to the participant’s desired sleep window in order to classify participants by chronotype: 1) phase advanced (falls asleep earlier than intended and wakes up earlier than intended); 2) phase delayed (falls asleep later than intended or wakes up later than intended); 3) phase neutral normal-riser (falls asleep and wakes up when intended); and 4) phase neutral early-riser (falls asleep when intended, but wakes up earlier than intended). Participants were then provided with a commercially available BLT device (Philips goLITE BLU) and provided with a personalized BLT schedule based on their chronotype and desired sleep window.

Each BLT dose was a recommended one hour duration, twice-daily for 20 weeks (i.e., weeks 5-24). There is no current consensus about duration or intensity of BLT [291], but preliminary evidence suggests all-day BLT may realign the circadian clock in older adults with cognitive impairment [2, 435]. Given the difficulty of enforcing all-day BLT outside a laboratory setting [435], we recommended one hour of BLT twice-daily and suggested participants get as much
Figure 7.2 Decision tree for bright light therapy prescription

- Determine if possible obstructive sleep apnea (OSA) risk
  - Use STOP-BANG Questionnaire to determine OSA risk
    - Low Risk: 0-2
    - Moderate Risk: 3-4
    - High Risk: 5-8

- High or Moderate Risk of OSA
  - Counsel participant to see physician about possible OSA

- Determine best asleep time and wake up time which works best with the participant’s schedule to attain 8 or more hours of sleep duration

- Determine if participant is sleep phase advanced, delayed, or neither based on their current sleep window and desired sleep window

- Participant has advanced sleep phase (i.e., falls asleep earlier than intended)
  - Morning bright light starts 2 hours after waking
  - Evening bright light ends a 12-hour day of light exposure
  - Light avoidance begins 1.5 hours before sleep window onset
  - Can continue normal light routine at night

- Participant is neither phased delayed or advanced (i.e., falls asleep when intended)
  - Morning bright light starts 2 hours after waking
  - Evening bright light ends 12-hour day of light exposure
  - Light avoidance begins 1.5 hours before sleep window onset
  - Can continue normal light routine at night

- Participant wakes up earlier than intended

- Participant wakes up when intended
  - Morning bright light starts 1 hour after waking
  - Evening bright light ends 12-hour day of light exposure
  - Light avoidance begins 2 hours before sleep window onset
  - Can continue normal light routine at night

- Participant has delayed sleep phase (i.e., falls asleep later than intended or wakes up later than intended)
  - Morning bright light starts 30 min after waking
  - Evening bright light ends 12-hour day of light exposure
  - Light avoidance begins 3 hours before sleep window onset
  - Total Light Avoidance
sunlight as possible between BLT doses during the day (while avoiding light after evening BLT dose and before morning BLT dose). We used a 12-hour interval between BLT doses in order to: 1) provide a strong time and behavioural cue for the hours the participant should be awake and out of bed (i.e., daylight hours); and 2) protect natural melatonin production in the 2-3 hours prior to sleep [2, 629, 630], while also providing a strong time and behavioural cue to promote sleep during the prescribed sleep window. Evidence supports such an approach—a recent RCT showed one hour of twice-daily BLT (12 hours between doses) improved subjective sleep among people living with Parkinson disease [434].

Participants also met with a certified fitness professional in week 5 to review their current PA level and develop an individually-tailored PA plan (Figure 7.3). The BAP approach was used to help participants develop their PA plan [402], and increase their PA to at least meet current PA guidelines of 150 minutes/week [631]. All certified fitness professionals were trained in motivational interviewing and use of BAP. Participants were provided with a Fitbit® Flex™ to be worn on the non-dominant wrist 24 hours/day. PA data from the device was wirelessly synchronized with the Fitbit online Dashboard, which was viewed only by the participants and their fitness professional. During weeks 5-24, the fitness professional reviewed each participant’s PA on the Dashboard and progressively modified activity goals during bi-weekly phone-calls. In instances where the participant failed to reach their PA goal during the previous two-week period, the participant was guided by the fitness professional to create new SMART goals (i.e., specific, measurable, achievable, realistic, and timely) for the next two weeks [402]. All participants were counselled to engage in PA ≥4 hours before their regularly scheduled bed time.
Figure 7.3 Decision tree for setting physical activity goals

PA level from CHAMPS and confirmation of activity level during interview

- < 3 Hours/Week of total walking time according to CHAMPS. Confirmed by interview.
  - Participants Categorized as Sedentary
    - Counseled to get >90 min of PA/week
    - Weeks 5-10
  - Counseled to get >120 min of PA/week
    - Weeks 10-15
  - Counseled to get >150 min of PA/week
    - Weeks 15-24

- 3-6.5 Hours/Week of total walking time according to CHAMPS. Confirmed by interview.
  - Participants Categorized as Somewhat Active
    - Counseled to get >120 min of PA/week
  - Counseled to get >150 min of PA/week
  - Weeks 15-24

- >6.5 Hours/Week of total walking time according to CHAMPS. Confirmed by interview.
  - Participants Categorized as Active
    - Counseled to get >150 min of PA/week
    - Weeks 10-15
7.2.6.2 Education (CON)

Participants in CON were invited to four group-based health enrichment lectures during weeks 1-4. During weeks 5-24, participants were asked to continue their normal activities and received monthly phone-calls wherein we queried about current health status and quality of life. At trial completion, CON participants received an abbreviated version of the intervention.

7.2.7 Measures

Outcomes were assessed at baseline, 12-weeks, and 24-weeks (primary endpoint). Baseline measurements included age, height using a wall-mounted stadiometer, and weight using a calibrated digital scale. General health and socioeconomic status was ascertained by questionnaire. Participants were surveyed at baseline for OSA risk using the STOP-Bang questionnaire,[632] general cognitive function using the MMSE and MoCA [457, 487], depressive symptoms using the Short Form Geriatric Depression Scale [633], and PA level using the CHAMPS questionnaire [149].

7.2.7.1 Primary outcome: objectively-measured sleep efficiency

The primary outcome measure was objectively-measured sleep efficiency (i.e., time asleep expressed as a percentage of time in bed), assessed using the MW8 [298]. Sleep efficiency was chosen as the primary outcome since it is the gold standard measure in evaluating insomnia treatment efficacy [634]. The MW8 data collection procedure is discussed in detail in elsewhere [137, 286, 375, 411]. Data were collected in 60 second epochs [452, 552]. Appendix F discusses how compliance to the MW8 protocol was determined. Participants were asked to wear the MW8
continuously for ≥14 days. MW8 data were subsequently downloaded and analyzed using MotionWare software 1.0.27 (CamNtech), which was used to estimate sleep efficiency.

### 7.2.7.2 Secondary sleep outcomes: objective and subjective sleep quality

The MW8 and MotionWare software was also used to estimate different parameters of sleep quality including: *sleep duration* (total time spent sleeping), *fragmentation index*, WASO (time spent awake after sleep has been initiated and before final awakening), and *sleep latency* (time between “lights out” and falling asleep). Fragmentation index is a description of restlessness while sleeping and is defined by MotionWare as the sum of 1) the total time spent sleeping categorized as *mobile* in the epoch-by-epoch *mobile/immobile* categorization expressed as a percentage of the time spent asleep; and 2) the number of *immobile* bouts which were equal to 1 minute in length expressed as a percentage of the total number of *immobile* bouts during time spent sleeping. Only minutes categorized as asleep were included in the calculation of fragmentation index. The MW8 provides validated estimates for each sleep quality metric [298]. In addition, subjective sleep quality was measured using the PSQI [299]. The PSQI has evidence of test-retest reliability among older adults at risk for dementia (ICC= 0.82) [300].

### 7.2.7.3 Secondary outcomes: cognitive function

We used the ADAS-Cog Plus as a global measure of cognitive function [454]. The ADAS-Cog Plus uses a multidimensional item response theory model which can flexibly utilize item scores from multiple cognitive assessment instruments to generate a global cognitive function score and standard error of measurement for that score. Higher scores indicate poorer cognitive performance. The ADAS-Cog Plus score was computed using the 13-item ADAS-Cog [456], MoCA [457], Trail
Making Test A and B [458], Digit Span Forward and Backward [459], and verbal fluency [458]. Detailed descriptions of the procedures used for these tests can be found in Appendix C.

7.2.7.4 Secondary outcomes: moderate-to-vigorous physical activity and sedentary behaviour

We also measured MVPA and SB using the MW8 [136]. For the current study, we used 60-second epochs [528]. Data were analyzed using MotionWare 1.0.27 (CamNtech). Data prior to recorded wake time on the first full day of recording were manually removed in order to only investigate full 24-hour recordings of activity. Thus, a participant with 14 nights of sleep recorded had 13 full days of activity recorded. Each day of activity consisted of when the participant self-reported being awake and out of bed. Participant self-report was confirmed via event marker time stamps from MW8 or the CSD.

A Microsoft Excel macro written by RSF (Appendix D) was used to reduce PA data to daily calculations of time spent in MVPA (i.e., ≥ 3.0 METs; [136]). We then calculated the percent of each day spent in MVPA (%MVPA). For example, if for a given day a participant was asleep from 12:00-6:00 AM, and went to bed the following evening at 10:00 PM, then we assumed that the participant spent 8 hours sleeping in a 24 hour period (i.e., 480 minutes). If this individual engaged in 100 minutes of MVPA, then the estimated %MVPA for that day would be:

\[
\frac{100 \text{ minutes of MVPA}}{960 \text{ minutes of wake time}} = 10.42\% \text{ of day spent in PA}
\]

The benefit of this approach is that it controls for differences in time which participants spent awake and out of bed.
7.2.8 Sample size

The sample size calculation was based on unpublished pilot data which suggested sleep hygiene education alone had a small effect on sleep efficiency after 6-months ($d=0.16$). Given the multicomponent nature of the INT, a larger effect size was assumed ($d=0.50$). Assuming a two-sided alpha of 0.05 and correlation across adjacent time points of 0.88 (estimated from pilot data), 40 participants per group would provide power of 0.85 to detect an effect size of $d=0.50$. To accommodate a potential drop-out rate of 15% as per past studies in our laboratory [199], 96 participants were recruited (48 per group).

7.2.9 Compliance and intervention adherence

Compliance to the CSD and MW8 protocol was monitored, as well as adherence to the BLT prescription and PA promotion program (Appendix F). Weekly PA was monitored for INT participants using the Fitbit online Dashboard. BLT adherence was recorded as percentage of prescription completed using calendars, and PA adherence as percentage of PA goal met.

7.2.10 Adverse events

Participants in INT were monitored for adverse effects throughout the course of the study during bi-weekly phone-calls. All adverse events were reviewed by the data safety monitoring board (JCD, LCL, and TLA). No adverse events were monitored in the CON group as it was an inactive control group.

7.2.11 Statistical analyses
All statistical analyses were conducted in R version 3.5.1 and followed the intention-to-treat principle (Appendix D). To address missing data at each time point, multiple imputation was performed in the *mice 2.46.0* package using predicted mean matching (40 imputations; 40 iterations each), and visually checked for convergence of the imputation model.

### 7.2.11.1 Primary analyses

Treatment effects were evaluated on the imputed data sets and between-group differences (INT vs. CON) in sleep quality were evaluated using mixed linear models with restricted maximum likelihood estimation. Time representing follow-up assessment (i.e., midpoint versus final) was included as a categorical fixed effect in addition to group and group x time interaction. The intercept was specified as a random effect and each model controlled for baseline outcome score. Unequal variance was allowed across time and group. Significance was set at \( p<0.05 \) and no adjustment was made for multiple comparisons, given this was a proof-of-concept RCT and Type II error is of more concern than Type I error [635]. Estimated marginal means, within group differences from baseline, and between group differences (INT – CNT) at 12-weeks and 24-weeks follow-up were calculated. Statistical estimates were pooled over the 40 imputed data sets using the Barnard-Rubin procedure to estimate pooled standard errors and degrees of freedom [636].

### 7.2.11.2 Secondary analyses

In addition to our primary analyses, we evaluated the relationship between changes in sleep quality (objective and subjective) and changes in cognitive function after 24 weeks using the imputed data sets. We created six separate models wherein changes in each measure of sleep quality was the major independent variable of interest and changes in ADAS-Cog Plus score was the dependent
variable. Each model included age, sex, baseline sleep quality, and treatment group as covariates of no interest. Significance was set at $p<0.05$ and no adjustment was made for multiple comparisons. Statistical estimates were pooled over the 40 imputed data sets using the Banard-Rubin procedure to estimate pooled standard errors and degrees of freedom [636].

7.3 Results

Ninety-six participants completed baseline assessment and were randomized, of which 88 completed the trial. Participant characteristics at baseline are described in Table 7.1. Mean age was 73 years (SD=5 years), 57% of participants were female, and participants reported engaging in 9.2 hours/week (SD=5.4 hours/week) of PA on the CHAMPS questionnaire. Mean sleep efficiency was 81.82% (SD=6.71%), duration was 404 minutes/night (SD=53 minutes/night), PSQI was 10.17 (SD=2.77), and average MoCA score was 22.52 (SD=2.36; range: 15 - 25) at baseline. Mean ADAS-Cog Plus score was -0.41 (SD= 0.55). Participants spent an average of 9.74% of the day in MVPA (SD= 6.67%).

Based on the STOP-Bang questionnaire results [632], six participants allocated to the INT group and four participants in the CON group had high OSA risk (i.e., scored >4 on the STOP-BANG). One INT participant with high OSA risk began using a CPAP after consultation with a physician.
Table 7.1 Participant characteristics at baseline (N= 96); mean (SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multimodal Chronotherapy (N=48)</th>
<th>Usual Care + Education (N= 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72 (5)</td>
<td>74 (5)</td>
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<tr>
<td>Females (n, %)</td>
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<td>32, 67%</td>
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<td>Education (n, %)</td>
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</tr>
<tr>
<td></td>
<td>8, 17%</td>
<td>5, 10%</td>
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<tr>
<td>Trade School or Some University</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>20, 42%</td>
<td>19, 40%</td>
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<tr>
<td>University Degree or Higher</td>
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<tr>
<td></td>
<td>20, 42%</td>
<td>24, 50%</td>
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<tr>
<td>Cognitive Function</td>
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<td>Mini Mental State Exam</td>
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<td>28.27 (1.26)</td>
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<tr>
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<td>22.44 (2.11)</td>
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<td>Chronotype¹</td>
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<tr>
<td>Phase Advanced</td>
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<tr>
<td></td>
<td>1, 2%</td>
<td>2, 5%</td>
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<tr>
<td>Phase Neutral Normal-Riser</td>
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<td></td>
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<td>12, 30%</td>
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<tr>
<td>Phase Neutral Early-Riser</td>
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<td></td>
<td>20, 43%</td>
<td>13, 37%</td>
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<tr>
<td>Phase Delayed</td>
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<td></td>
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<td>16, 28%</td>
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<td>CHAMPS Physical Activity (Hours/Week)²</td>
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<td>9.5 (6.4)</td>
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<td>Sleep Quality</td>
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<tr>
<td>MW³ Sleep Efficiency (%)</td>
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<td>406 (51)</td>
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<td>MW³ Fragmentation Index</td>
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<td>-0.42 (0.53)</td>
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<tr>
<td>%MVPA⁴</td>
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<td>10.27 (6.83)</td>
</tr>
</tbody>
</table>

¹ Determined from participant desired sleep window and actigraphy determined sleep onset. *Phase Advanced* = fall asleep earlier than intended or wake up earlier than intended; *Phase Neutral Normal-Riser* = fall asleep when intended and wake up when intended; *Phase Neutral Early-Riser* = fall asleep when intended but wake up earlier than intended; *Phase Delayed* = fall sleep or wake up later than intended.

² Measured using the Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire

³ MotionWatch8©

⁴ Percent of the day spent in MW8 measured moderate-to-vigorous physical activity
7.3.1 Primary outcome: sleep efficiency (objective)

Participants complied with the MW8 protocol on 71% of all nights of observation. Results of the linear mixed models are described in Table 7.2. Compared with CON participants, those in the INT group did not have statistically better sleep efficiency at 24-weeks follow-up (estimated mean difference: 0.99%; 95% CI [-0.75, 2.73]; p=0.268).

7.3.2 Secondary outcomes: objective and subjective sleep

As detailed in Table 7.2, there were no significant differences between groups at 24-weeks for the objective measures of sleep duration (estimated mean difference: 3.26 minutes/night; 95% CI[-10.37, 16.90]; p=0.635), fragmentation index (estimated mean difference: -2.79; 95% CI[-5.99, 0.41]; p=0.087), latency (estimated mean difference: -1.28 minutes/night; 95% CI[-4.42, 1.87]; p=0.421), and WASO (estimated mean difference: -3.57; 95% CI[-14.20, 7.06]; p=0.506). There was a significant group difference in PSQI at 24-weeks follow-up (Estimated mean difference: -1.47; 95% CI [-0.22, -2.72]; p=0.024).

7.3.3 Secondary outcomes: cognitive function

As described in Table 7.2, there were no significant differences between groups in cognitive function at either 12-weeks (estimated mean difference: -0.01; 95% CI[-0.17, 0.15]; p=0.931) or 24-weeks follow-up (estimated mean difference: -0.14; 95% CI[-0.02, 0.31]; p=0.081).
Table 7.2 Estimated marginal means and standard errors for changes in sleep quality, cognitive function, moderate-to-vigorous physical activity, and sedentary behaviour at baseline, 12 weeks, and 24 weeks follow-up by group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Multimodal Chronotherapy</th>
<th>Usual Care + Education Group</th>
<th>Between Group Differences (Intervention Minus Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>12 Weeks</td>
<td>24 Weeks</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sleep Efficiency (%)</em></td>
<td>81.18 (7.93)</td>
<td>81.63 ± 0.49</td>
<td>81.73 ± 0.69</td>
</tr>
<tr>
<td>Secondary Outcome: Objective Sleep Quality¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Sleep Duration (min/night)</em></td>
<td>400.83 (56.13)</td>
<td>400.19 ± 5.47</td>
<td>414.02 ± 5.04</td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td>35.53 (14.99)</td>
<td>33.71 ± 0.97</td>
<td>33.48 ± 1.20</td>
</tr>
<tr>
<td><em>Sleep Latency (min/night)</em></td>
<td>6.33 (5.49)</td>
<td>7.99 ± 0.92</td>
<td>8.42 ± 1.03</td>
</tr>
<tr>
<td>WASO (min/night)²</td>
<td>93.98 (44.78)</td>
<td>90.75 ± 2.73</td>
<td>94.22 ± 4.19</td>
</tr>
<tr>
<td>Secondary Outcome: Subjective Sleep Quality³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>PSQI Total Score</em></td>
<td>9.85 (2.59)</td>
<td>7.17 ± 0.45*</td>
<td>6.46 ± 0.46*</td>
</tr>
<tr>
<td>Secondary Outcome: Cognitive Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>ADAS-Cog Plus</em></td>
<td>-0.39 (0.57)</td>
<td>-0.56 ± 0.06*</td>
<td>-0.58 ± 0.06*</td>
</tr>
<tr>
<td>Secondary Outcome: Percent Moderate-to-Vigorous Physical Activity (%MVPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%MVPA</td>
<td>9.19 (6.50)</td>
<td>9.19 ± 0.40</td>
<td>9.38 ± 0.48*</td>
</tr>
</tbody>
</table>

Note: All models controlled for baseline outcome of interest.
* Within group significantly different from baseline ($p< 0.05$)

1 Measured using MotionWatch® wrist-worn actigraphy
2 Wake-After-Sleep-Onset
3 Pittsburgh Sleep Quality Index
7.3.4 Relationships between changes in sleep quality and changes in cognitive function

Figure 7.2 describes the relationships between changes in sleep quality and changes in cognitive function. There were no significant relationships between changes in sleep quality and changes in cognitive performance for objectively-measured sleep efficiency ($\beta = 0.006 \pm 0.009; p = 0.531$; pooled $R^2 = 0.008$), duration ($\beta = -0.001 \pm 0.001; p = 0.419$; pooled $R^2 = 0.011$), fragmentation index ($\beta = 0.001 \pm 0.006; p = 0.930$; pooled $R^2 = 0.003$), latency ($\beta = 0.004 \pm 0.006; p = 0.556$; pooled $R^2 = 0.007$), WASO ($\beta = 0.003 \pm 0.003; p = 0.319$; pooled $R^2 = 0.015$), and PSQI ($\beta = -0.001 \pm 0.015; p = 0.949$; pooled $R^2 = 0.003$).

7.3.5 Compliance and intervention adherence

Adherence rates to the individually-timed BLT prescription and PA promotion program are described in Appendix F. Ninety-one percent of all BLT calendars were returned. Average participant adherence to the BLT prescription over the 20-week BLT program was 65% to the morning BLT dose, and 59% to the evening BLT dose. Average participant adherence to the PA program over 20 weeks was 73%.

7.3.6 Adverse events

Three adverse events occurred in the INT group during the study. One participant reduced the intensity of the BLT light because of headaches. Another participant needed to stop BLT due to irritation in the eyes—potentially due to retinal surgery which occurred prior to study entry. Another participant was counselled by a physician to stop BLT because of macular degeneration. In these two instances, participants continued with the intervention, but did not perform BLT.
Figure 7.4 Relationships between changes in sleep quality and changes in cognitive function over 24 weeks

Higher scores are indicative of improvement for all models. All models included age, sex, baseline sleep quality, and treatment group as covariates of no interest. There were no significant associations between changes in sleep and changes in cognitive function across all six models. All models controlled for age, sex, baseline sleep quality, and treatment group. Pooled $R^2$ for the major IV are included.
7.3.7 Secondary outcomes: moderate-to-vigorous physical activity and sedentary behaviour

Changes in %MVPA are described Table 7.2. There were no significant differences between groups in %MVPA at either 12-weeks (estimated mean difference: -0.35; 95% CI[-1.45, 0.75]; \( p=0.526 \)) or 24-weeks follow-up (estimated mean difference: 0.07; 95% CI[-1.29, 1.43]; \( p=0.921 \)).

7.4 Discussion

Poor sleep is a common problem for older adults with MCI, however few treatment options are available [2]. This proof-of-concept study is the first to test whether a lifestyle intervention of multimodal chronotherapy can improve objective and subjective sleep quality in older adults with probable MCI and poor sleep.

There were no statistically-significant differences in objective sleep quality. However, an examination of the confidence intervals around the between-group differences in the primary outcome (sleep efficiency) plausibly suggests a ~3% improvement to a ~1% deterioration relative to the control condition at 24-weeks follow-up. This aligns with the results of a preliminary meta-analysis (N=3), which suggest multimodal chronotherapy can improve sleep efficiency by 3.44% (95% CI: [0.89, 5.99] [448]; however, these data are based on samples of older adults with dementia. Future trials with larger samples are thus required to provide a more precise treatment effect.

There were statistically-significant improvements in subjective sleep quality, as measured by the PSQI. It is possible that self-reported sleep quality provides an important and distinct source of
information in comparison to objective measures. Sleep is a complicated phenomenon and recent evidence suggests objective and subjective indices measure different components of older adult sleep [286]. Specifically, subjective sleep quality according to the PSQI and CSD appear to be poorly correlated with actigraphy-measured sleep, and the lack of relationship between objective and subjective sleep measures appears to be unrelated to age, sex, education, or cognitive status. Subjective sleep may thus represent a distinct component of sleep, which can be targeted through chronotherapy.

Current evidence suggests BLT and PA can promote older adult subjective sleep quality. Two separate quasi-experimental BLT interventions found that older adult’s subjective sleep quality improved after 6 days, with no change in objective sleep quality [432, 433]. Twice-daily BLT improved subjective sleep quality in adults with Parkinson’s disease [434]. The extant literature also consistently shows that increasing PA improves the subjective sleep quality of older adults; in contrast, the effect of PA on older adult objective sleep quality is inconsistent [365]. Sleep hygiene education does not appear to have a consistent effect on either subjective or objective sleep quality [421], however current best practices suggest combining sleep hygiene education with other therapies [425].

Interestingly, we did not find that improvements in any measure of sleep quality were associated with improvements in cognitive function. While the relationship between sleep and cognitive function is well documented [296], surprisingly little is known about whether improving sleep can lead to improvements in cognitive function. The most clear evidence that improving sleep quality can protect and promote cognitive function comes from the treatment of OSA using CPAP and
other behavioural therapies [637]; however, OSA causes hypoxia in the brain such that the alleviation of hypoxia is likely able to restore cognitive health [638, 639]. While poor sleep quality due to insufficient sleep, fragmented sleep, reduced sleep depth, or subjective feelings about sleep are all likely to have some negative impact on cognitive function [560, 640, 641], it is unclear whether therapies which improve any aspect of sleep quality can help promote cognitive function. Pallier and colleagues [642, 643] determined in two separate studies that drug management of sleep-wake cycles in a transgenic mouse model of Huntington’s disease—a disease which is characterized in the later stages by highly disrupted sleep [644]—can improve cognitive function. Mizuno and colleagues [645] determined that the administration of donepezil in people living with AD improved time spent in REM sleep, as well as increased sleep efficiency and decreased sleep latency. Moreover, increases in REM sleep were associated with improvements in cognitive function. While these results are promising, it is unclear whether non-pharmacological therapies to improve sleep can also promote cognitive function.

We also did not determine that our intervention significantly improved %MVPA. Participants were highly active at baseline, engaging in ~9 hours/week of total PA according to the CHAMPS, and spending ~9% of the day in MVPA according to the MW8. Using our criteria for determining PA goals described in Figure 7.3, most of our participants were thus classified as active at baseline and thus were counselled to get ≥150 minutes/week of PA. Hence, most of our participants were likely counselled to maintain their PA level rather than increase their PA. It is thus plausible that the high PA level of our participants may have limited the effects of the PA intervention to improve sleep. Indeed, the greatest benefits of PA on a multitude of health outcomes occur when a sedentary individual becomes more physically active [631]. Future research should thus examine whether
less active older adults with MCI might benefit more from our multimodal chronotherapy intervention.

Therefore, the collective evidence suggests BLT and PA can improve subjective sleep quality, but whether these therapies also promote objective sleep quality and cognitive function is less clear. Both poor objective and subjective sleep are associated with cognitive decline [646], and thus improvements in either may benefit cognitive health.

7.4.1 Limitations

This study did not measure sleep architecture. Both MW8 and PSQI have evidence of validity against PSG [298, 453], but the agreement of actigraphy with PSG is lower in individuals with poor sleep compared to those with good quality sleep [556, 647]. There is no validated minimal clinically important difference for either actigraphy-measured sleep quality or for the PSQI.

Self-reported sleep quality might be more susceptible to expectation effects of improvement in a study of this kind in which participants cannot feasibly be blinded to treatment condition. While twice-daily BLT may be beneficial for promoting sleep quality among populations with cognitive impairment [2, 434, 435], current recommendations for promoting circadian regulation suggest: 1) morning BLT for phase-delayed individuals; and 2) evening BLT for phase-advanced individuals [430]. There are no current recommendations for BLT for people who are phase-neutral. Participants were highly active at baseline, and thus it is unlikely that increases in PA would improve either objective or subjective sleep quality. Indeed, we did not find that the intervention significantly increased %MVPA.
No circadian markers were measured in this study. More precise estimates of circadian phase may be necessary to accurately time BLT with the biological clock [291, 430]. Calendars tracking BLT adherence are subject to recall bias. Finally, given the multimodal design of our intervention, it cannot be easily determined which aspect of the intervention had the greatest effect on sleep quality.

7.4.2 Conclusion

This study determined that multimodal chronotherapy can improve subjective, but not objective, sleep quality in older adults with MCI and poor sleep. However, the intervention did not significantly improve cognitive function, and improvements in sleep were unrelated to improvements in cognitive function. Future research is needed to determine which components of chronotherapy are most effective, as well as the long-term feasibility of multimodal chronotherapy for improving sleep.
Chapter 8: General discussion

In the six preceding chapters, I presented data acquired from observational and experimental studies examining how each time-use activity behaviour (i.e., PA, SB, and sleep) can impact older adult cognitive health. The observational studies (Chapters 2-5; [375, 411, 522]) indicate that PA, SB, and sleep have a dynamic relationship with each other and older adult cognitive health. On the other hand, the experimental studies (Chapters 6 and 7; [648]) do not indicate that directly intervening on time-use activity behaviours can improve older adult cognitive health.

The aim of this chapter is to summarize and integrate the information I have provided throughout Chapters 2-7 [375, 411, 522, 648]. I will provide a brief synopsis of each study included in my dissertation (Section 8.1), revisit the research questions proposed in the first chapter (Section 8.2), and discuss limitations (Section 8.3) and future directions (Section 8.4).

8.1 Study synopses

Chapter 2 [522] was a systematic review of observational studies which examined whether SB is associated with poorer cognitive function. Six of eight studies reported an association between SB and poorer cognitive performance in later life. The studies used eight different measures of SB (mostly subjective measures) and 13 different measures of cognitive function. These results indicate that SB is associated with lower cognitive performance, but the attributable risk of SB to all-cause dementia incidence is unclear, given that no prospective cohort study has yet to examine the relationship of SB with dementia incidence. Moreover, the heterogeneity in the methods used to measure SB and cognitive function make it difficult to determine the precise magnitude of this relationship.
Chapter 3 [411] was a cross-sectional study which examined whether there were differences in the associations of objectively-measured PA and SB with cognitive function based upon probable MCI status. I also investigated whether there were differences in PA and SB levels between older adults with probable MCI and those without. I reported differences in the relationships of PA and SB with cognitive function for older adults with probable MCI, as compared to those with healthy cognitive function. Older adults with probable MCI were less active and more sedentary than their healthy cognitive peers. These results suggest that there are underlying differences in the relationships of PA and SB with cognitive function for older adults with MCI as compared with those without MCI.

Chapter 4 [375] was a cross-sectional study which assessed the independent relationships of objectively-measured PA and: 1) objectively-measured sleep; and 2) subjectively-measured sleep with older adult cognitive function. The study also examined the relationships of objectively-measured PA with objective and subjective sleep. The results from the latent variable modeling analyses indicated that objectively-measured PA was associated with cognitive function independent of any measure of sleep, and objectively-measured sleep efficiency was also independently associated with older adult cognitive function independent of PA. There were no associations between PA and older adult sleep—neither for objective or subjective measures of sleep. These results suggest that PA and sleep are each associated with older adult cognitive function, but are related to cognitive performance through independent mechanisms.

Chapter 5 used baseline data from a six-month proof-of-concept RCT among older adults with knee osteoarthritis (NCT02315664) to cross-sectionally examine the independent relationships of
objectively-measured MVPA and objectively-measured SB with cerebral cortical thickness. Using a cluster-wise correction method for structural MRI analyses, I determined that objectively-measured MVPA was associated with greater cortical thickness in the temporal pole and superior frontal gyrus of the left hemisphere independent of SB. Contrary to my original hypothesis, I did not find that objectively-measured SB was associated with cortical thickness independent of MVPA. These results indicate that any consequences of SB on brain structure might be mollified by high MVPA levels.

In Chapter 6 [648], a secondary analysis from the same six-month proof-of-concept RCT (NCT02315664) described above, I examined the effect of an intervention to increase MVPA and reduce SB among older adults with knee osteoarthritis. The aim of this secondary analysis was to determine the effects of the intervention on cognitive function. I determined that while this intervention increased objectively-measured MVPA by 27 minutes/day compared to the control group after 2 months, it did not improve cognitive function. Furthermore, there were no associations between changes in MVPA and SB with changes in cognitive function. As these adults with knee osteoarthritis were highly active and cognitively healthy at baseline, I concluded that increases in MVPA and reductions in SB among highly active older adults are unlikely to significantly improve older adult cognitive function.

Chapter 7 was a proof-of-concept RCT (NCT02926157) to determine whether a multimodal personalized chronotherapy intervention consisting of 1) individually-timed BLT; and 2) health coaching to promote PA, in conjunction with general sleep hygiene education, could improve sleep and cognitive function among older adults with probable MCI. I determined that the intervention
significantly improved the subjective sleep quality of older adults with probable MCI, but did not significantly impact objective sleep. The intervention did not improve cognitive function, and changes in sleep quality were unrelated to changes in cognitive function. These results indicate that multimodal chronotherapy can promote the subjective sleep of older adults with MCI. However, it is unclear whether multimodal chronotherapy can promote objective sleep, and whether therapies to improve the sleep of older adults with MCI can help promote cognitive function.

8.2 Revisiting the main research questions

In Section 1.7.1, I highlighted each of the research questions which my thesis investigated:

1. How are time-use activity behaviours associated with older adult cognitive health?
2. What is the dynamic relationship between time-use activity behaviours and older adult cognitive health?
3. Can we promote cognitive health in older adults with and without cognitive impairment through targeted interventions on time-use activity behaviours?

I will now revisit each of these questions, and provide a concluding remark for each.

8.2.1 Question #1: How are time-use activity behaviours associated with older adult cognitive health?

For simplicity, I have broken this section into two parts. I will first discuss how each time-use activity behaviour is associated with older adult cognitive health (Section 8.2.1.1). In Section 8.2.1.2, I will discuss how these relationships might change based on cognitive status.
8.2.1.1 Relationships of time-use activity behaviours with older adult cognitive health

As I discussed in detail throughout Chapter 1, there is a large and growing body of evidence which indicates that regular PA is an important pillar of healthy cognitive aging [5, 102]. Evidence also indicates that sufficient sleep quality and quantity is important for older adult cognitive health [4, 326]; however, I noted in Chapter 1 that there was only preliminary evidence which suggested SB is associated with poorer cognitive health [6, 7].

Chapter 2 [522] of my thesis thus extends the current knowledge about how SB is associated with older adult cognitive health by providing an exhaustive review of the current literature on the association between SB and cognitive function. As discussed in Chapter 2 [522], my research suggests that SB is associated with poorer cognitive function. However, the heterogeneity of measures used to assess SB and cognitive function, along with the paucity of studies (N= 8) which have examined this topic, prevented me from determining the magnitude of the association.

Upon further reflection and a broader consideration of the current literature, I suggest that the magnitude of this relationship is likely small-to-modest—at the very least, smaller in magnitude than the association between PA and cognitive health. Indeed, the relationship between PA and cognitive health is likely small-to-modest in size. Northey and colleagues determined that exercise training had a modest effect on older adult cognitive function ($d= 0.29; [154]$). A recent systematic review and meta-analysis I conducted also found that the effect size of exercise training on older adult cognitive function is modest ($g= 0.24; [648]$). Given that exercise training is a sub-category of PA which involves planned and structured PA (usually MVPA) in order to increase fitness [92],
it seems unlikely that lifestyle PA which does not exert the same volume or intensity of energy expenditure as exercise training will have a stronger effect on cognitive function.

This is not to say that lifestyle PA does not benefit cognitive health. The epidemiological evidence suggests that regular PA is a pillar of healthy cognitive aging and can significantly reduce the risk of cognitive decline and dementia [5, 156, 173, 210, 617]. However, given that the effects of lifestyle PA on cognitive function are likely modest, it seems more plausible that regular lifestyle PA (with perhaps the exception of exercise training, which likely has more robust effects on cognitive health [83, 154]) is neuroprotective and a preventive measure against cognitive decline rather than a therapeutic strategy for restoring cognitive health.

It is also unlikely that SB has a larger effect on older adult cognitive health than PA. Briefly, most adults engage in SB for greater than 7 hours/day independent of PA level [649]; older adults spend less than 20 minutes/day in MVPA according to population wide estimates in the United States and Canada [96, 650]. If the mechanisms by which PA and SB impact cognitive health are the same as current evidence indicates [6, 7, 271], it seems more likely that the less frequent and more energetically expensive behaviour would have a stronger association with older adult cognitive health. Hence, the association between SB and cognitive health is likely to be quite small.

I also expect that the relationships of sleep quality and quantity with older adult cognitive health to be small-to-modest in size—something which current evidence supports. In a recent systematic review and meta-analysis of 18 longitudinal studies, Shi and colleagues determined that sleep disturbances (defined as insomnia or OSA) were associated with a 19% greater risk of developing
all-cause dementia [651]. A sub-analysis indicated that the relative risk of dementia was similar irrespective of whether sleep was measured objectively or subjectively. As discussed throughout my thesis, sleep changes as a function of age [296]. While poor sleep is certainly a risk factor for cognitive decline [2], more than 50% of older adults report having at least one chronic sleep complaint [323]. The historical record also suggests poor sleep has been a part of the human experience since well before the modern era [652]. In Shakespeare’s *Henry IV*, a full soliloquy is dedicated to the woes of poor sleep in old age. The aging, troubled, and sleep deprived title character bemoans:

> How many thousand of my poorest subjects  
> Are at this hour asleep! O sleep, O gentle sleep,  
> Nature’s soft nurse, how have I frightened thee.  
> That thou no more wilt weigh my eyelids down  
> And steep my senses in forgetfulness?

*Henry IV Part II* (3.1.4-8)

If anything, the anthropological evidence suggests that most modern humans living in developed nations are experiencing longer and better objective sleep than at any time in human history [275, 276, 653]. In a particularly interesting cross-cultural analysis, Samson and colleagues [654] determined that the Hadza – an equatorial hunter-gatherer community in Tanzania – have shorter objective sleep duration and efficiency, and more fragmented sleep than two samples of healthy controls from Italy and the United States. However, 95% of Hadza participants (N= 37; aged 18-65 years) reported that they slept enough, 92% of respondents indicated that they fell asleep...
quickly, and 0% indicated that they suffered sleeping problems. Hadza participants also had significantly better markers of circadian regulation compared to their post-industrial counter-parts.

Most humans in post-industrial societies are substantially less active than their modern day hunter-gatherer counterparts [655, 656]. If there is an evolutionary mismatch in behaviour between the modern world and the Pleistocene era that humans evolved from [657], it seems that our PA behaviour is more likely mismatched to our modern environment than our sleep. Sleep research in post-industrial, non-Western populations also illustrates that there is no “normal sleep pattern” [658]. At the very least, it cannot be assumed that there is a universal formula of objectively “good sleep” which will help promote cognitive health.

I have also noted throughout this thesis that objective and subjective sleep describe different aspects of the multi-dimensional nature of sleep [286], and it is surely possible that subjective sleep quality is a stronger predictor of older adult cognitive health than objective sleep quality. However, the epidemiological record which has investigated the relationship between subjective sleep and cognitive health is mixed. A systematic review and meta-analysis by Lo and colleagues [659], determined that both long (i.e., > 9 hours/night) and short self-reported sleep duration (< 6 hours/night) increased the odds of poorer cognitive health. Another systematic review examining the association between subjective sleep and older adult cognitive function determined that there was no consistent relationship between subjective sleep quality and older adult cognitive function—although the authors noted that there was considerable heterogeneity in how sleep and cognitive function were assessed across the 29 studies [660]. Some literature suggests older adult
subjective sleep quality is as good or better than younger adults [661]. It is also unclear whether poor subjective sleep is associated with cognitive performance independent of objective sleep.

Although what constitutes good sleep is not easily defined, it remains plausible that sleep architecture may play a critical role in older adult cognitive health—particularly SWS (i.e., stages 3 and 4). SWS helps promote the clearance of Aβ that accumulates during wake-time [356], and combats oxidative stress (which is linked to AD pathology) by enhancing cellular restitution processes [9]. There are also small subtle changes in sleep architecture which are a natural consequence of the aging process [532], which appear to mirror the slow dulling in cognitive abilities which occur as adults age [27]. These data suggest sleep architecture is closely associated with cognitive health in later life [662]. This idea is intriguing, however natural changes in sleep architecture are an unavoidable consequence of human aging [663]. All humans need sleep [664], but do natural changes in sleep architecture throughout life constitute a threat to older adult cognitive health? Of this, I am skeptical.

Human evolutionary biology suggests an alternative hypothesis for why both sleep and cognitive health decline in later life. Briefly, there is growing consensus from the paleontological record that human lifespan began to increase substantially in length ~2 million years ago [665]. Human lifespan is significantly longer than any other primate, and humans are unique in having a prolonged post-reproductive lifespan [666-669]. Even among modern day hunter-gatherers, despite having a life expectancy of under 40 (driven mainly by high infant and juvenile mortality), the average modal adult life span is ~72 years of age [670]. Chimpanzees, our closest living relatives, have modal lifespan of 15 years and a life expectancy of ~30 years [671]. Human brain
size—and likely our cognitive abilities—has undergone an even more dramatic change than lifespan over the course of hominid evolution [672]. Human brains are ~2.5 times larger than the brains of the great apes [673]; brain size and longevity have long been recognized as interrelated in mammals [674]. Humans also have dramatically different sleep patterns from other primates [275]. In comparison to other primates, human sleep is shorter, deeper, and exhibits higher proportion of REM sleep than expected.

Each of these changes in human biology (i.e., increased longevity, larger brain size and increased cognitive capacity, and more intense sleep patterns) likely evolved due to selective pressures on our hominid ancestors. While retrospective hypotheses about human evolution are difficult to empirically test and may be biased by the fossil record, two hypotheses for increased human longevity stand out. The grandmother hypothesis suggests that the evolution of a long lifespan is the result of selection acting on grandmothers and their ability to provide resources for their kin [668, 675, 676]; that is, post-reproductive humans without young offspring to care for could provide increased foraging effort for their offspring’s children, thus increasing evolutionary fitness. A second hypothesis suggests that natural selection acted to extend the lifespan because of the necessity of extensive early life learning, with this delayed maturation for increased learning paying off in the form of increased reproductive fitness [677]. This embodied capital hypothesis is based upon the understanding that human hunter-gatherer techniques require extensive time to learn [667]. Allen and colleagues have since proposed that the selection pressures for increased brain size and cognitive abilities, and their maintenance well-past reproductive years, may have been important in selection for increased lifespan through the promotion of intergenerational social support networks [672].
The more efficient sleep patterns of humans, in comparison to other primates, is also believed to have been based on selective pressures including: 1) increased predation risk in terrestrial environments (i.e., sleeping on the ground as opposed to in trees); 2) threats from rival groups of humans; and 3) benefits arising from increased social interaction [275]. Hunter-gather societies, which represent our closest approximation of ancestral hominid lifestyles [678], also display sleep patterns that support the *sentinel hypothesis* [679]; whereby, in order to reduce the risks of sleeping, hunter-gatherers share the task of vigilance during sleep with some individuals sleeping while others remain awake. Importantly, older hunter-gatherers are more likely to act as sentinels during the early morning hours and have shorter sleep durations compared to other group members [680], suggesting the utility of reduced sleep for older adults in the ancestral past.

Based on these current models for the development of longer lifespan, increased brain size and cognitive capacity, and more intense sleeping patterns [275, 672], I suggest one possible explanation for the evolutionary fitness benefits of shorter and lighter sleep among older adults. As illustrated in Figure 8.1, brain structure and function develop rapidly in the early years of life and continue to increase until the third decade of life [681]. These changes in brain structure and function are accompanied by increases in both fluid intelligence and crystallized intelligence [682]; fluid intelligence typically peaks in late adolescence and then progressively declines beginning around age 30 or 40, while crystallized intelligence grows throughout most of adulthood. Sleep is dominated by REM and SWS in early life [683]—most likely because of the benefits of REM and SWS on learning and memory [279, 684]. However, REM and SWS durations decline throughout life; REM decreases significantly in the neo-natal period and then is
relatively stable until older adulthood, while SWS duration begins to decreases around age 30 [683].

**Figure 8.1 Hypothetical model for the relationships of brain and cognitive health with sleep across the lifespan**

Adapted from Walhovd et al., 2016 [681]; Li et al., 2004 [682]; and Ohayon et al., 2004 [683].

Given that fluid and crystallized intelligence about complex and skill-intensive food acquisition techniques would be critical to the survival of early human ancestors [685], it is likely that high REM and SWS which can promote learning and memory are prioritized during the long developmental period characteristic of humans in order to increase survival chances. Early humans who reached old age would have high crystalized intelligence of food acquisition strategies which they could transfer information about to their progeny.
However, the evolutionary pressure would be lower for ancestral older humans to learn new food acquisition skills—especially since their physical capacities would be lower than younger group members. In addition, ancestral older humans likely played a critical role as sentinels throughout the early morning hours [680], providing younger group members with increased opportunities to sleep. Given the low evolutionary pressure for the acquisition of new skills, plus the critical role ancestral older humans would play in ensuring group survival by having short sleep, there was likely selective pressure for older ancestral humans to have shorter and lighter sleep than younger group members. Moreover, it is likely that older adults in the Pleistocene era also played a critical role in the transfer of knowledge from generation to generation, and hence there would be selective pressure to maintain this knowledge in older adulthood. It thus seems more likely that there is a functional weakening in the relationship between sleep architecture and cognitive health in older adulthood that has its roots in human evolutionary biology.

However, this hypothesis cannot explain why poor sleep in older adulthood is associated with poorer cognitive health. In Section 8.2.2, I will provide a potential explanation based on the results of my other thesis studies examining the dynamic relationships of time-use activity behaviours with each other and cognitive health.

8.2.1.2 Cognitive status as a moderator of the relationships of time-use activity behaviours with older adult cognitive health

It is also plausible that the relationships between time-use activity behaviours and cognitive function change based on cognitive status (e.g., MCI vs. healthy cognition). As I noted in Chapter 1, underlying neurobiological differences likely exist between older adults with MCI and those
without MCI [2], such that a functional change in the relationships of health behaviors with cognitive function may occur in MCI [296].

Chapter 3 [411] illustrates that there are indeed differences in how time-use activity behaviours are related to older adult cognitive health based on cognitive status. Specifically, I found that older adults with MCI are less active and more sedentary than their healthy cognitive peers [411]. There are two possible explanations for these results. One explanation is that older adults with MCI have been less active and more sedentary throughout their lives, both of which are risk factors for cognitive impairment in later life [156, 522]. It is also plausible that changes in cognitive status can influence PA and SB through diminished executive function [19, 36, 482]. Loss of executive function capability is associated with poorer independence and functionality [331, 534, 536], and changes in executive function can predict changes in activity levels [537-539].

I also determined that the relationships of PA and SB with older adult cognitive function depend on cognitive status, such that the relationships of PA and SB with older adult cognitive function is attenuated among older adults with MCI [411]. In Chapter 3 [411], I proposed two possible explanations. The first potential reason for this finding is that older adults with MCI may not meet a minimum threshold level of PA (or exceed a maximum threshold of SB) which may lead to nonsignificant associations between these time-use activity behaviours and cognitive function. This interpretation of my findings may also help explain why PA in the form of exercise training for older adults with MCI can lead to significant improvements in cognitive function by providing a necessary threshold level of PA and concomitant reduction in SB [185, 201].
However, as I described above, the relationship between SB and cognitive function is likely smaller than the association of PA and cognitive function, and thus it is unlikely that changes in SB would elicit a similar response. Another issue with this proposed threshold effect can be found in Chapter 7, wherein participants (all of whom had MCI) were highly active at baseline according to the CHAMPS questionnaire and most participants were already classified as *active* according to our criteria for determining activity level.\(^1\) In a post-hoc analysis, I did not determine that there were significant relationships for %MVPA (\(\beta= -0.006 \pm 0.008\)) and %SB (\(\beta= 0.001 \pm 0.004\)) with cognitive performance—which appears to provide some initial confirmation of the results I found in Chapter 3 [411]. If the sample from Chapter 7 was considered active, why then would PA and SB still not be associated with cognitive function?

The second explanation I provided in Chapter 3 [411] for why the associations of PA and SB with cognitive function appear to be attenuated in people with MCI thus appears more reasonable. Specifically, there are likely underlying neurobiological differences between those with MCI and those without [541]. For example, compared to older adults without MCI, those with MCI have greater amounts of Aβ accumulation [39], accelerated atrophy of the medial temporal lobe [40], and decreased functional connectivity [46]. These underlying changes in the MCI brain may thus potentially alter the relationships of time-use activity behaviours with cognitive function [2], leading to an attenuation of the relationships of PA and SB with cognitive function [296].

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\(^1\) Non-MCI participants in Chapter 3 still had higher %MVPA (\(p= 0.03\)) and lower %SB (\(p= 0.01\)) than MCI participants in Chapter 7 in a post-hoc analyses. There were no significant differences in %MVPA and %SB between the two groups of MCI participants.
Although my thesis did not directly examine how cognitive status may alter the relationships between sleep and cognitive health, there is at least preliminary evidence that cognitive changes (either due to injury or illness) can alter this relationship. I recently found that individuals with chronic stroke (i.e., >1 year since incidence) exhibited significantly poorer sleep quality and cognitive function than an age- and sex-matched control group [686]. Moreover, differences in cognitive performance between older adults with and without stroke were accentuated in the presence of poor sleep quality. I also include in Appendix G recent analyses (currently under minor revision in *Sleep Science and Practice*) from the Sleep and Cognition study (used for Chapters 3 and 4; [286, 375, 411]), which indicate that compared to older adults with healthy cognitive function, older adults with MCI exhibit: 1) lower subjective and objective sleep duration after adjusting for age, sex, sleep medication use; and 2) less consistent objective sleep patterns from night-to-night. Given that older adults with MCI have poorer sleep than their healthy cognitive counterparts [346, 623], it seems reasonable that underlying neurobiological changes in the MCI brain might also influence the relationship of sleep with cognitive health. It is thus possible that declines in sleep quality in the normal aging process that have a small impact on cognitive health become more serious and far more sinister when cognitive status changes. Indeed, poor sleep might be a proverbial canary in the coal mine—such that significant changes in sleep quality might signal underlying neurobiological changes that are indicative of cognitive decline [687].

8.2.2 Question #2: What is the dynamic relationship between time-use activity behaviours and older adult cognitive health?
As I highlighted in Figure 1.3, time-use activity behaviours are each distinct behaviours, but share a complex relationship with each other. This is in part because each of these behaviours are intricately linked through the circadian sleep-wake cycle [4]. However, most research into how time-use activity behaviours are associated with older adult cognitive health has failed to examine the potential dynamic associations between these behaviours and older adult cognitive health. For example, it is still unclear whether these behaviours are associated with cognitive health simultaneously, synergistically, or in silos.

Researchers are beginning to understand that these behaviours are inextricably linked with each other [3, 362], although there is still debate about how to examine the relationships of time-use activity behaviours with older adult cognitive health. As I argued in Section 1.4.1, the simplest and most parsimonious approach to addressing how these behaviours are associated with cognitive health is to use GLM to examine the relationships of each time-use activity behaviour with cognitive health independent of other time-use behaviours. This approach is at least a first step towards understanding how these behaviours are associated with each other and older adult cognitive health.

Chapter 4 [375] thus investigated how PA and sleep are associated with older adult cognitive function independent of each other. In addition, I examined whether PA is associated with better sleep among older adults. The results suggest that PA is associated with better older adult cognitive function independent of sleep quality. Only sleep efficiency is associated with better cognitive performance independent of PA, and no measure of older adult sleep quality was associated with PA. These results appear to align with current research that suggests that PA and sleep efficiency
are both associated with older adult cognitive health [156, 377, 560-562]. However, it remains unclear how PA and sleep efficiency interact to promote cognitive health. Recent evidence suggests sleep efficiency may mediate the relationship between PA and cognitive function [377], results which seem to provide further support for the restoration hypothesis—whereby energy expenditure from PA increases sleep need [364]. While I did not test a mediation effect of PA and sleep efficiency, the results indicate that in addition to a potential mediation effect, it is possible that PA and sleep efficiency are associated with cognitive health through independent mechanisms.

Importantly, the results of this study also suggest that PA can mitigate the potentially negative implications of poor sleep on cognitive function. As I suggested in Section 8.2.1, PA likely has a stronger association with older adult cognitive health than does sleep; however, I also noted that the evolutionary hypothesis that I proposed could not explain why shorter and lighter sleep in older adulthood appears to have negative side-effects on cognitive health [662].

One plausible reason for why older adults’ sleep would be less important for their cognitive health during early human evolution is that ancient humans were highly physically active. Much like modern day hunter-gathers, our evolutionary ancestors (i.e., hominids including *H. erectus, H. habilis*, and early *H. sapiens*) had to perform vast amounts of PA in order to obtain food and avoid predators [688]. The fossil record indicates that a change in body shape occurred during the evolution of the genus *Homo* which differs from the more ape-like body shape of earlier hominins [689, 690]. This upright body posture was critical for foraging and for hunting, allowing ancestral humans the ability to travel long distances (both by walking and running) in order to obtain food sources [689, 691]. Raichlen and Alexander hypothesized that the high PA and cognitive demands
of the hunter-gather lifestyle was a selective pressure towards ancient humans evolving to significantly benefit from PA [692]. This is an interesting idea, although humans are not the only mammal to benefit substantially from PA [179, 180], and the evolution of human cognitive capacity and brain size appears to have occurred over millions of years in a somewhat chaotic process [693, 694]. There is also good evidence that the social demands of primate society in conjunction with changes in diet during early hominid evolution were more likely the selective pressures that increased human cognitive capacity and brain size [695-698]. Regardless, modern day hunter-gathers such as the !Kung of Botswana and the Ache of Paraguay walk an average of 9 to 20 km/day [655]. Most individuals living in western society—even those who meet PA guidelines—are far less active [656].

Coupled with this evidence, recent genomic analyses suggest that early humans were all homozygous APOE-ε4 allele carriers [699]. Carriers of the ε4 allele have higher levels of total cholesterol and accumulation of atherosclerotic plaques in arteries, leading to increased risks of cardiovascular disease and stroke, as well as dementia and AD [700]. Importantly, APOE-ε4 is associated with the progression of sleep/wake disturbances [701], and APOE-ε4 can significantly exacerbate the consequences of poor sleep [702]. The ε2 and ε3 alleles confer reduced risks, however these are relatively recent additions to the human genome, having evolved by about 200,000 years ago [699]. Given the genetic constraints of APOE-ε4, in order for early humans to have reached older adulthood (with healthy cognition, nevertheless) such that they could transfer important survival knowledge to the younger members of their group, it seems likely that the high amounts of PA necessary for survival in the Pleistocene era would have reduced the potential negative effects APOE-ε4 [703]. Indeed, longitudinal studies indicate that low PA in APOE-ε4
carriers is associated with an increased risk of developing dementia or AD [477], and APOE-ε4 carriers who are more physically active at midlife have greater protection against dementia or AD ~20 years later than APOE-ε4 non-carriers [704]. In much the same way, high amounts of PA could have helped promote sleep in earlier life by promoting recovery and restoration [364], while high PA in later life could offset the negative side-effects that shorter and lighter sleep could have on health. Indeed, recent cross-sectional evidence also indicates that PA attenuates the negative detriments of poor sleep on cognitive function [568]. It thus appears that regular PA may help maintain older adult cognitive health even when sleep quality is poor.

The results from Chapter 4 [375] also appear to be at odds with past research on the relationship between PA and sleep, given there is ample evidence that PA helps people sleep better [4, 11, 365]. However, there are two important caveats which bear mentioning. First, meta-analytic data suggests that relationship between PA and sleep attenuates with age, such that the benefits of PA on sleep are smaller for older adults than for younger adults [365]. This is likely because of underlying changes in older adult neurobiology such as neural atrophy, nocturnal hypoxia, neuroendocrine changes, and altered neuromodulation which may reduce the potential for PA to promote sleep [296]. Second, the strongest evidence indicating that PA is associated with sleep comes from RCTs wherein the intervention is PA in the form of exercise training [4]. Given that PA in the form of exercise training is typically more energetically expensive than most other types of PA [92], it seems reasonable that larger amounts of energy expenditure would have greater impacts on sleep—as is suggested by the restoration hypothesis [364]. Hence, the relationship between PA and older adult sleep is likely small.
While Chapter 4 [375] did not directly examine the independent relationships of SB and sleep with older adult cognitive function, I performed a post-hoc analyses on the data in Chapter 4. Specifically, I examined whether 1) SB was associated with cognitive performance independent of sleep, and vice versa; and 2) SB was associated with poorer sleep. The results (Appendix H) suggest that there is no relationship between SB and cognitive performance independent of sleep quality, nor is there a relationship between SB and sleep. Sleep efficiency was still associated with cognitive performance independent of SB. This seems to suggest that SB has less of an influence on cognitive performance independent of sleep quality than PA, and that SB is not associated with sleep quality. These results should not be altogether unsurprising. It is unlikely that small changes in SB would influence sleep quality, given that SB is energetically inexpensive and most adults in the developed world are sedentary for greater than 7 hours/day [8, 649].

There is also little known about the independent associations of PA and SB with older adult cognitive health; particularly, whether PA and SB are independently associated with better brain health. Chapter 5 provides preliminary evidence that MVPA is associated with greater cortical thickness independent of SB in regions of the brain that are prone to atrophy and are associated with cognitive decline [44, 45, 705]. However, the results do not indicate that SB is associated with cortical thickness independent of MVPA, further illustrating that high amounts of MVPA may be neuroprotective against the deleterious effects of SB. While it is unclear whether all types and intensities of PA are neuroprotective, irrespective of the amount of time spent in SB, there is at least some recent evidence which indicates higher amounts of LPA (i.e., 1.5-3.0 METs), such as household chores, may help maintain brain health [168]. These data thus collectively suggest that high amounts of PA can promote cognitive health independent of sedentary time.
8.2.3 Can we promote older adult cognitive health through targeted interventions on time-use activity behaviours?

There are an increasing number of meta-analyses which show that PA in the form of exercise training can significantly improve cognitive function [83, 102, 154]; however, as I have suggested above, the effects of PA on cognitive health are likely small-to-modest in size. In the first meta-analysis on this topic, Colcombe and Kramer [102] suggested that the effect of exercise training on cognitive function has a standardized mean difference of \( d = 0.31 \). While these initial results were promising, a Cochrane-based systematic review by Young and others determined that exercise training did not improve cognitive performance among healthy older adults [540]. More recently, Northey and colleagues [154] found that the improvement in cognitive function from exercise training was smaller \( (d = 0.29) \) than originally suggested by Colcombe and Kramer [102]; the authors also determined that exercise training had similar effect sizes on cognitive function for older adults with MCI \( (d = 0.28) \), and those without \( (d = 0.36) \). I have since performed a meta-analysis that suggests the effect of exercise on cognitive function is likely smaller than what was suggested previously by Colcombe et al. [102] and Northey et al. [154], with a conservative estimate of Hedge’s \( g = 0.24 \). Unlike past meta-analyses on this topic, I used Hedge’s \( g \) to calculate effect sizes and variances for all outcomes because it provides a small sample bias correction to Cohen’s \( d \) [706, 707], hence the more conservative effect-size estimates. In this meta-analysis the effect size for older adults with MCI \( (g = 0.25) \) was similar to that for older adults with healthy cognition \( (g = 0.31) \) [83]; these estimates are slightly more conservative than those of Northey and colleagues \( (MCI: d = 0.28; \text{non-MCI: } d = 0.36) \). While I also determined that the effect on primary cognitive outcomes \( (g = 0.36) \) was larger than for secondary cognitive outcomes \( (g = 0.15) \), these
data suggest that the effect of exercise training on cognitive function for older adults is likely small-to-modest in size.

However, it is important to note that exercise training is meant to increase or maintain one or more aspects of fitness [92], while performing PA of any type may (or may not) improve fitness. Most forms of exercise training (including AT, RT, and MT) expend enough energy to be classified as MVPA [107], however most interventions to increase lifestyle PA and MVPA have small effects on PA behaviour \( (d = 0.19 \text{ to } 0.26; [708, 709]) \). Indeed, in a meta-analysis by Conn and colleagues [709], the authors determined that the effect size was consistent with a mean difference of 496 ambulatory steps/day between the treatment and control participants. The authors indicated that this magnitude of change is not enough to meet public health goals of 10,000 steps/day [710, 711]. Given the small expected improvements in PA from most lifestyle interventions, small changes in PA are unlikely to lead to large improvements in older adult cognitive health.

Interestingly, Chapter 6 [648] provides evidence that even larger changes in MVPA among healthy older adults may have a small effect on cognitive function—particularly among cognitively healthy older adults who are already meeting current PA guidelines. While the intervention significantly increased daily MVPA by 26.6 minutes/day [145], I did not determine that there were significant improvements in cognitive function following the intervention, nor did I determine that intervention-associated improvements in MVPA were associated with improvements in cognitive function [648]. As I highlighted in the chapter, participants were already quite active at baseline (mean objectively-measured MVPA was 29.2 minutes/day) and thus increases in MVPA may have had a small effect on an already active group. The large-scale, evidence-based, and rigorous LIFE
study RCT also successfully increased objectively-measured MVPA by 40 minutes/week compared to the control group [712], but the intervention did not significantly improve cognitive function [616]. Participants in the LIFE study were also highly active at baseline (mean objectively-measured MVPA was ~198 minutes/week), and a sub-group analysis determined that individuals in the intervention who were older and had poorer physical function (and likely worse cognitive function given the links between physical and cognitive function [713]) did significantly improve their cognitive performance compared to the control.

These data appear to suggest that increasing MVPA can benefit older adult cognitive health in individuals who are significantly underactive, but increasing the MVPA of highly active older adults (i.e., currently meeting or exceeding MVPA guidelines) does little to improve cognitive health. This seems to align with the current understanding of the dose-response effect of PA on health. For example, Lee and colleagues [714] determined that there was an inverse-relationship between increasing PA and reduced health risks such that meeting current PA guidelines was associated with a significant 20-30% reduction in the risk of all-cause mortality; further reductions in risk were observed with increasing amounts PA, although these reductions were smaller. A meta-analysis on the dose-response relationship between PA and risk of coronary heart disease also found that meeting current PA guidelines of 150 minutes/week had a 14% lower risk of coronary heart disease, while engaging in ≥300 minutes/week of PA reduced the risk of heart disease by 20% [715]. The authors also determined that even small amounts of PA were associated with reduced risk of coronary heart disease, further supporting current PA recommendations that 1) some PA is better than none; and 2) additional benefits occur with more PA [90, 439, 631]. Xu and colleagues [171] recently conducted a preliminary meta-analysis investigating the dose-
response relationship between self-reported PA and cognitive health, wherein they found that for every 500 kcal/week of energy expenditure from PA, there was a 10% and 13% decrease in the risk of all-cause dementia and AD, respectively. While these recent data are preliminary, Chapter 6 [648] does provide further support that the benefits of PA on cognitive health are likely largest for underactive – and perhaps cognitively impaired – individuals. Further increasing PA for individuals who are already highly active might thus have little effect on cognitive health.

The results from Chapter 6 [648] also appear to indicate that reducing SB likely has a very small effect on cognitive health—at least smaller than the effect of PA. The intervention did not significantly reduce SB, and there were no significant relationships between intervention-associated decreases in SB and improvements in cognitive performance [648]. Current evidence suggests PA and SB share a similar physiological mechanism by which they impact older adult cognitive health [6, 7, 271], and thus it seems likely that the more energetically expensive behaviour (i.e., PA) will have a larger effect on cognitive health. If the effect size of increasing PA on older adult cognitive health is indeed small, then it stands to reason that reducing SB has an even smaller effect.

There is also evidence that lifestyle interventions can improve older adult sleep [2, 398], although it is not clear whether improving sleep also improves cognitive health. Current meta-analytic data suggests that CBT interventions can have moderate-to-large improvements on global sleep quality, latency, efficiency, and WASO in older adults with insomnia [398]. Sleep hygiene education – a component of CBT – does not appear to have a consistent effect on sleep [421, 424], however current guidelines suggest it be included in lifestyle interventions to promote sleep [416, 430]. PA
and exercise training may also improve sleep, but the effects of PA on sleep weaken with age [365]. Another potential lifestyle intervention with preliminary evidence is chronotherapy, such as BLT and timed PA [2]. However, the effectiveness of chronotherapy as a strategy to improve sleep and circadian rhythms is largely uncertain [448]. Interventions to promote sleep using BLT have had mixed results [2], and PA as chronotherapy is also still in its infancy [449]. While the potential of chronotherapy as an intervention is still relatively unknown, a recent meta-analysis (N= 3) by O’Caoimh and colleagues suggested that combining BLT, PA, and sleep hygiene education could significantly improve the sleep of older adults with cognitive impairment [448]. No evidence to date has examined whether improving sleep through lifestyle intervention can significantly improve older adult cognitive health.

Chapter 7 thus expands upon the preliminary evidence about how to improve the sleep of older adults with MCI. I determined that a multimodal chronotherapy intervention of 1) individually-timed BLT; and 2) health coaching to promote PA, in conjunction with general sleep hygiene education, could significantly improve some aspects of sleep in older adults with MCI and poor sleep. While the intervention successfully improved the subjective sleep of older adults with MCI, I did not determine that there were any significant improvements in objective sleep following the 6 month intervention. Moreover, I did not determine that improvements in sleep were associated with improvements in cognitive performance on the ADAS-Cog Plus.

As I have discussed throughout this thesis, sleep is a complicated phenomenon that is both physiological and psychological. Lifestyle interventions (particularly CBT) have been successful at improving the physiological sleep of older adults [398], although the evidence is mixed about
whether BLT and PA can promote physiological sleep [365, 431]. In all likelihood, the effect of chronotherapy consisting of BLT and PA on older adult physiological sleep is small. In the meta-analysis by O’Caoimh and colleagues [448], the authors found that multimodal chronotherapy interventions to improve the sleep of older adults with cognitive impairment increased sleep efficiency by ~3% per night. Assuming that older adults dedicate 8 hours each night (i.e., 480 minutes) to trying to sleep, this would increase total sleep time by a paltry 14.4 minutes. Multimodal chronotherapy interventions are also quite burdensome for participants. Is it likely that an individual will commit to daily 1) timed exposure to bright light; and/or 2) PA at precise times for the rest of their lives? Even if multimodal chronotherapy could substantially improve sleep, I think it highly improbable. Our current evidence about the long-term effectiveness of PA interventions suggests that long-term and consistent behavioural changes to lifestyle are unlikely [445-447].

This does not mean that sleep is unmodifiable without pharmacology. CBT is a highly effective method for improving the sleep of all adults including a meta-analytic estimated 1) 2.31 point improvement on the PSQI (95% CI: [-4.24, -0.38]); and 2) PSG-measured 29.14 minute decrease in WASO (95% CI: [-52.61, -5.67]) and 6.46% increase in sleep efficiency (95% CI: [2.83, 10.08]) [716]. Another meta-analysis by Irwin and colleagues [398] also estimated moderate-to-large effects of CBT on global sleep quality \(d= 0.79\), sleep efficiency \(d= 0.74\), WASO \(d= -0.69\), and latency \(d= -0.50\). Given that CBT is the frontline approach for treating insomnia [717], it seems reasonable that it should be included in any non-pharmacological strategy to improve sleep. Other non-pharmacological treatment strategies for sleep complaints may help augment the benefits of CBT; however, it seems unlikely that even the most-effective dose of PA or most well-
timed chronotherapy intervention is likely to have an effect on sleep that is comparable to CBT. Future interventions aiming to improve the sleep of older adult adults through lifestyle intervention should thus determine the effectiveness of combining CBT with other potential therapies to improve sleep.

Yet, it is currently unknown whether improving sleep can promote cognitive health. The results from Chapter 7 do not indicate that changes in sleep are associated with changes in cognitive performance. There were no significant relationships between changes in any measure of sleep and changes in cognitive performance. I discussed in Section 8.2.1.1 that my thesis results and human evolutionary biology suggest that sleep likely has a smaller relationship with cognitive health in normal (i.e., healthy) older adulthood than it does in early life. In Section 8.2.1.2, I then suggested that underlying neurobiological changes that occur in MCI might alter the relationship of sleep with older adult cognitive health, such that sleep problems might have a more nefarious impact on cognitive health in cognitively impaired individuals than in older adults with healthy cognition. I then proposed in Section 8.2.2 that the very high PA levels of ancient older adults might have protected against the deleterious consequences of poor sleep on older adult cognitive health. Using this rationale, how could participants from Chapter 7 – most of whom I classified as highly active according to the CHAMPS – that received multimodal chronotherapy still not improve in cognitive performance even though the intervention significantly improved their sleep?

There are several explanations, in my opinion. First, as I have highlighted throughout my thesis, physiological sleep is different than psychological sleep [286]. It is thus possible that improvements in psychological sleep, as I found in Chapter 7, do not necessarily benefit cognitive
Physiological sleep (particularly SWS and REM) promotes learning and memory [279, 359], while psychological sleep does not appear to have a consistent impact on any particular aspect of cognitive performance [659, 660]. Physiological changes in sleep may thus be necessary to elicit changes in cognitive performance.

A second possible explanation is that small improvements in sleep may not be sufficient to elicit improvements in cognitive function. The magnitude of the effect of the multimodal chronotherapy intervention on sleep ranged in size from a Cohen’s $d = 0.22$ for PSQI score, to $d = 0.04$ for sleep latency. Thus, while changes in sleep may elicit changes in cognitive performance, improvements in sleep might need to be sufficiently large in order to elicit cognitive changes.

A third possibility is that there may be a long temporal lag in how sleep can promote cognitive health. As highlighted by Jack and colleagues [61] and summarized in Figure 1.1, the hypothesized biological cascade for dementia first occurs with slow accumulation of neurophysiological markers associated with dementia (i.e., increases in Aβ burden, neurofibrillary tangles, inflammation, etc.); these changes in neurophysiology can then lead to changes in brain structure and function, and cognitive function. Given that sleep promotes clearance of these neurophysiological markers from the CNS [356], while poor sleep is associated with greater amounts of these markers in the CNS [9], it is plausible that improved sleep promotes better neurophysiology. However, if the time-course of cognitive decline is as slow as suggested by Jack and others [61], then improvements in neurophysiology from better sleep probably take longer than 6 months for cognitive benefits to occur.
While each of these three explanations (or some combination thereof) appear plausible, my thesis cannot yet answer whether improving sleep can promote cognitive health among people with MCI. Indeed, this is a largely unexplored field and the preliminary results of Chapter 7 only provide initial evidence about how improving sleep can impact cognitive health; however, future research is needed to determine whether targeting the sleep of older adults is indeed a worthwhile strategy for promoting healthy cognitive aging.

8.3 Limitations

The limitations of the studies included in this thesis have been discussed in the respective chapters. In this section, I will provide the general limitations which should be considered.

8.3.1 General limitations

Chapters 3-5 [375, 411] were cross-sectional studies, and thus I cannot attribute causality to any of the findings—they are all associations. The sample size in Chapter 5 was relatively small because of the cost of neuroimaging. Participants in Chapters 5-7 [648] were likely healthier than their peers given their desire to take part in an intervention which included an incentive (i.e., a Fitbit) which would be attractive to physically active individuals. Participants in Chapters 3 [411], 4 [375], and 7 were also likely experiencing poorer sleep than their peers since each of these studies used recruiting advertisements that discussed sleep, and Chapter 7 was an intervention to improve sleep. MCI is typically diagnosed using the Petersen criteria [19]: 1) subjective cognitive impairment; 2) objective cognitive impairment according to a MoCA score of <26/30; 3) no functional impairment in activities of daily living; and 4) no dementia. However, I did not use a clinical diagnosis of MCI in Chapters 3 [411] or 7, but rather classified individuals as MCI solely
based on a MoCA score of <26/30. All participants were likely free of dementia as they all had an MMSE score of >24/30 [487].

None of the outcome measures used in Chapters 6 [648] or 7 currently has a MCID [718]. Briefly, MCID is defined as the smallest difference in score in a domain of interest which patients perceive as beneficial and which would mandate in the absence of troublesome side effects and excessive costs, a change in a clinical management of a patient [719]. The lack of a MCID for any of my measures of time-use activity behaviours or cognitive health limits the ability of researchers to discern between what is statistically significant and what is clinically relevant. A final limitation is the setting for Chapters 3-7 [375, 411, 522, 648]. British Columbia is the most physically active province in Canada, with currently 64% of British Columbia residents meeting the PA guidelines according to the British Columbia Ministry of Health [588]. Only 13.1% of all Canadian older adults meet the PA guidelines of 150 minutes/week of MVPA [650], and thus it is possible that the findings from Chapters 3-7 [375, 411, 522, 648] are not generalizable—given the high PA level of the participants in these chapters.

### 8.3.2 Measurement of physical activity limitations

There are several important limitations in this thesis regarding the measurement of PA. Throughout my thesis I have objectively-measured PA as an outcome variable using either the MW8 or the SWA. While each of these measures have evidence of validity and reliability for measuring older adult PA [136, 137, 143, 720], they do not capture all aspects of PA.
The MW8 also likely overestimates actual time spent in MVPA. For example, average %MVPA in Chapters 3 [411] and 4 [375] were 10.25% and 9.91%, respectively. Assuming that the average participant was awake and out of bed for 16 hours each day (i.e., 960 minutes/day), then mean daily MVPA for participants in Chapters 3 [411] and 4 [375] was ~98 minutes/day and ~95 minutes/day, respectively. Current estimates suggest that older adults are on average far less active, and less than 15% of all older adults in Canada and the United States currently meet the PA recommendations of 150 minutes/week of MVPA [96, 650]. In addition, the sensitivity-to-change of wrist-worn accelerometers (including the MW8) is unclear.

I did not include subjective PA as an outcome in any of my thesis studies, although I did use the CHAMPS questionnaire in Chapter 7 to classify participants as active, somewhat active, or sedentary. Subjective PA may capture important information about PA context and type [373], which might be related to older adult cognitive health. The CHAMPS may also not capture all aspects of PA and has a tendency to overestimate PA level [147, 148], and may also be open to self-report biases—especially among individuals with MCI who may have difficulty accurately recalling their PA [114].

### 8.3.3 Measurement of sedentary behaviour limitations

I only estimated SB using the MW8 and SWA, each of which has several limitations. While the MW8 and SWA provide estimates of energy expenditure [136, 137, 143, 720], they do not provide information about body position. In addition, the MW8 is only a biomechanical measure, while the SWA is a biomechanical and thermodynamic measure; neither device is a behavioural measure of SB (i.e., subjective measure), and thus the MW8 nor SWA can provide important information
about the context in which SB occurs. This may be especially critical since different types of SB (e.g., cognitively stimulating activities such as computer use) may have different associations with cognitive function [475-477]. Finally, little is known about the sensitivity of the MW8 to changes in SB.

### 8.3.4 Measurement of sleep limitations

None of my thesis studies measured sleep structure, which might provide the best approximation for how sleep impacts (and is associated with) older adult cognitive health. While there is at least preliminary evidence of validity for the MW8 [298, 450, 451], there is not yet criterion evidence of validity for the MW8 in older adults. There are substantial changes which occur in sleep schedules, sleep architecture, and other aspects of sleep quality from early older adulthood to later older adulthood [296, 321, 322], and it is possible that younger-older adults may have significant differences in sleep-wake patterns compared with the older-older adults. These differences in sleep-wake patterns may require different measurement protocols. Although all event-marker time stamps were confirmed with the CSD to determine when a participant was awake and out of bed according to current actigraphy guidelines [552], it is possible that the last awakening during each sleep window did not coincide with the time participants got out of bed. Sleep latency is also difficult to measure using actigraphy, given that individuals with poor sleep tend to lie in bed motionless, but awake, for longer periods of time [721-723]. It is also unclear how sensitive the MW8 is to changes in sleep.

There are also a few important limitations to the PSQI. Most importantly, the PSQI has a low correlation with sleep estimates using the MW8 [286], suggesting that these measures estimate
different aspects of sleep. It is also unclear whether cognitive impairment may reduce the validity and reliability of the PSQI for measuring subjective sleep. In any case, subjective measures of sleep are open to issues of recall bias and improvements in self-reported sleep from interventions are open to social-desirability bias [285]. Finally, none of my thesis studies examined markers of circadian physiology. Circadian rhythms are closely tied to the regulation of the sleep-wake cycle [4], and may play an important role in how sleep effects cognitive health [2].

8.3.5 Measurement of cognitive health limitations

Throughout my thesis I have only measured two domains of older adult cognitive health: 1) cognitive function; and 2) brain structure. None of my thesis studies measured brain function or neurophysiological biomarkers, and thus the conclusions of my thesis studies in regards to these domains of cognitive health should be treated with caution.

There are also several important limitations to how I measured cognitive function. While the ADAS-Cog Plus has evidence of validity and reliability [530], and provides a flexible measure of global cognitive function, few studies have used it as an index of older adult cognitive health. The paucity of studies which have used the ADAS-Cog Plus limit the generalizability of findings and the interpretability of results. Moreover, it is still unclear how sensitive the ADAS-Cog Plus is to changes in cognitive performance. The ADAS-Cog Plus also was designed using the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort [724], and thus cognitive scores generated from the ADAS-Cog Plus might only be suitable to individuals who would be eligible for inclusion in ADNI. Finally, in Chapter 6 [648] I measured cognitive function using two measures from the NIH toolbox [461-463]; however, these measures only provide information on two specific
domains of cognitive function (executive function and memory). Chapters 3 [411], 4 [375], and 7 focused on global cognitive function, and thus the results from Chapter 6 [648] may only be applicable to two specific domains of cognitive function.

The use of structural neuroimaging is also susceptible to several important constraints, due to a lack standardized protocols—which are a side product of constantly evolving techniques as well as advancements in neuroimaging technology. One of these constraints is the cluster-forming threshold I adopted ($p < 0.05$) in Chapter 5; the cluster-wise threshold I adopted is very liberal in comparison to a previous analysis using this analytical approach [580]. In addition, structural MRI data can also be influenced by data processing procedures (e.g., skull stripping, motion correction, etc.) and the degree to which manual edits are made to the data. It is thus suggested to be parsimonious with manual editing in order to limit influence on the data. Chapter 5 also only examined one aspect of brain structure, and thus the results of this study should be treated with caution since other aspects of brain structure may not have the same associations with MVPA and SB.

### 8.3.6 Interpretation of the results using Darwinian Medicine

Throughout Chapter 8, I have used current theories from Darwinian Medicine in order to interpret the results. Briefly, Darwinian Medicine attempts to use the theory of evolution by natural selection to explain aspects of disease and behaviour [657]. This is helpful in distinguishing the ultimate causes of behaviour (i.e., *why* a behaviour occurs) from the proximate causes of behaviour, or *how* a behaviour occurs [725]. Human evolutionary history can thus explain the underlying causes of behaviours in the modern world, and how these behaviours can negatively
affect our health [726, 727]. However, the current understanding of human evolution is based entirely on retrospective analyses and hypotheses, and also the fossil record. It is entirely possible that as new fossils are discovered, current theories for the evolution of the human species will change. Moreover, it is impossible to know for certain what the evolutionary determinants and pressures were for the development of specific human traits, nor is it completely clear how different genes may have shaped human evolutionary history. Given these limitations, the evolutionary hypotheses I have promulgated in this thesis should be treated with caution until more data emerges which can confirm (or refute) these ideas.

8.4 Future directions

This section offers guidance for future research aimed to examine how time-use activity behaviours can impact older adult cognitive health. For clarity, I will discuss each of the following major topics separately: 1) the impact of each time-use activity behaviour on older adult cognitive health (Section 8.4.1); and 2) the dynamic relationships of time-use activity behaviours with older adult cognitive health (Section 8.4.2).

8.4.1 The impact of each time-use activity behaviour on older adult cognitive health

8.4.1.1 Physical activity

The precise prescription of PA for cognitive health is still elusive, and it is unclear whether this prescription needs to be modified for individuals with a higher risk of dementia. It is unclear whether there are indeed underlying neurobiological changes which occur in MCI that alter the relationships between PA and older adult cognitive health. Future research should address whether
there is indeed a functional weakening in the relationships between PA and cognitive health in individuals with MCI.

More research is also needed to address whether different types and intensities of PA can impact different aspects/domains of cognitive health, or if the effects of PA on cognitive health are broad in nature. For example, current evidence suggests PA can positively impact the cognitive domains of global cognitive function, executive function, and memory [5, 173]; however, it is unclear whether different types and intensities of PA can have differential effects on these aspects of cognitive function.

Research has also yet to determine whether fitness or PA level is more important for cognitive health. Fitness and PA level are only loosely related [589, 728], and it is unclear whether high PA or high fitness is more important for cognitive health. Future research should thus determine whether PA is associated with cognitive health independent of fitness, and vice versa. It is also important to consider how genetic differences might impact the effect of PA on older adult cognitive health, and whether certain genetic polymorphisms (e.g., APOE) can impact this relationship.

The recent debate surrounding which aspects of cognitive function are impacted by PA and exercise training has also raised another important question. Briefly, it has been suggested that more cognitively engaging PA and exercise training (e.g., martial arts, sport, exergaming, etc.) will have larger effects on cognitive health than traditional methods of promoting PA and/or increasing fitness through exercise training [207, 209]. Raichlen and Alexander also hypothesized
that humans have adapted to respond to more cognitively engaging PA, such that these types of PAs would provide the greatest benefit to cognitive health [692]. This idea is interesting and is worth further consideration, although I find it unlikely that the human mind is a blank slate during traditional modes of exercise. If anything, recent fMRI studies during PA suggest that there is a high degree of brain activation which increases in signal strength as the intensity of exercise increases [729].

Lastly, the role of biological sex as a potential moderator of the efficacy of PA and exercise training needs further inquiry [730]. Two recent meta-analyses indicated that the effects of exercise training on cognitive function (particularly for executive function and memory) may be larger for females than for males [187, 188]; my own recent meta-analysis suggested that sex does not significantly impact the effect of exercise training on cognitive function [83]. However, meta-analyses examining the disaggregated sex-specific effects of exercise are still needed.

8.4.1.2 Sedentary behaviour

While the work I have conducted in my thesis suggests that SB has a small effect on older adult cognitive health, there are still several important unanswered questions which require further consideration. First, there have been few studies designed to specifically address whether reducing SB can promote older adult cognitive health. To my knowledge, there is one RCT which is currently being conducted which will examine as a secondary outcome whether reducing SB can improve cognitive function [731]; however, more research is needed to determine whether reducing SB alone can impact older adult cognitive health.
At the present time, it is clear that there is indeed a relationship between SB and poorer cognitive health; however, the precise magnitude of this relationship is unclear. Future research will need to determine the precise risk that excessive SB has on older adult cognitive health.

8.4.1.3 Sleep and circadian rhythms

It is unclear if poor sleep is a causal factor in the progression of dementia, or if the pathophysiology of dementia is responsible for declines in sleep quality. One of the primary reasons that the temporality and directionality of this relationship is yet unclear is that elucidating this relationship would require a long-term prospective longitudinal study which observes the changes in sleep quality from early life into old age. At the very least, future prospective studies should investigate changes in sleep quality and cognitive function from mid-life onward.

Few interventions have been performed to promote sleep among individuals at risk for cognitive decline. For example, there has not yet been an intervention which has examined the benefits of CBT on older adults with MCI—and whether improvements in sleep from CBT can improve cognitive health. It is also unclear whether improving subjective sleep, objective sleep, and/or sleep architecture provides similar (or differential) benefit to cognitive health. Additionally, little research has investigated sex differences in sleep and whether biological sex moderates the impact of sleep on cognitive health.

Far less is known about how circadian rhythms can impact cognitive health. Although sleep is closely tied to circadian function, it is unclear whether it is poor sleep or circadian dysregulation that is linked to cognitive decline. In addition, chronotherapy interventions are only in their
infancy, and more research is needed to determine whether this is indeed a viable strategy to promote sleep and cognitive health [449].

8.4.1.4 The dynamic relationships of time-use activity behaviours with cognitive health

Research is still needed to determine the relationships of PA with older adult sleep structure. In addition, there is very little evidence about how SB is associated with older adult sleep, and thus future work will need to investigate if there is indeed a relationship. Furthermore, the independent relationships of PA and SB with older adult sleep are yet unclear.

The strongest evidence indicating that PA can improve sleep quality comes from RCTs of exercise training, however, there have been remarkably few studies of older adults [365]. Moreover, there has been little research conducted to determine whether increasing MVPA (or reducing SB) is a viable option for improving sleep.

Results from a recent meta-analysis indicate that the relationship between PA and sleep quality may be attenuated in older adults [365]. However, it is unclear whether this is due to a functional weakening in the relationship between PA and sleep quality as adults age [376], or if there are underlying changes in older adult neurobiology which reduce the potential to impact sleep quality through strategies such as PA [296].

While my thesis work has helped to provide initial evidence about how PA, SB, and sleep may impact older adult cognitive health through convergent and divergent mechanisms, it is still unclear whether each of these behaviours impact cognitive health simultaneously, in synergy, or
Future work should examine whether improvements in sleep from increased PA (or exercise training) mediates the impact of PA on cognitive health, or whether PA moderates the impact of sleep on older adult cognitive health—or vice-versa.

8.5 Conclusion

Maintaining the cognitive health of older adults will be one of the major public health challenges for decades to come, as the total number of older adults worldwide continues to increase with each year and a cure for dementia remains elusive [15]. Increasing older adult PA, reducing SB, and improving older adult sleep and circadian regulation appear to be viable strategies for maintaining older adult cognitive health. In addition, there is growing evidence that PA can positively impact older adult sleep and circadian alignment, and there is at least preliminary evidence that PA and sleep may improve cognitive health through multiple mechanisms—both convergent and divergent. A critical next step is to determine whether increasing PA (or reducing SB) can be used to protect older adult sleep as a primary prevention strategy for dementia. In addition, research is required to determine the most potent prescription of PA and SB for maintaining older adult sleep health and cognitive health.
References


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Appendix A: Cognitive domain criteria and classification of common cognitive function measures

1. **Global Cognitive Function** - Tasks which examined multiple domains of cognitive function including memory, executive function, and processing speed.

   **Measures:** 3MSE, ADAS-Cog, MMSE, MoCA, MoCA-Korean Version, RBANS Global Cognitive Score, 5 Cog Test: Clock Drawing Task, 5 Cog Test: Analogy Task, Raven Standard Progressive Matrices, Block Design Task, Mental Control Task, Wechsler Adult Intelligence Test, RIPA, Cattell’s Matrices

2. **Executive Function** - A broad set of thinking abilities which includes planning, set-shifting, working memory, and inhibition.


3. **Memory** - A broad set of thinking abilities which include spatial memory, immediate memory, and episodic memory.


4. **Processing Speed** - Measures reaction time and ability to process information quickly
Appendix B: Evidence of validity and reliability for the MotionWatch8® wrist-worn actigraph for measuring physical activity, sedentary behaviour, and sleep

Table 1. Cut-points for sedentary behaviour, light physical activity, and moderate-to-vigorous physical activity using the MotionWatch8

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>Cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>d²</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>≤ 178.50</td>
<td>0.78</td>
<td>0.70</td>
<td>0.70</td>
<td>0.22</td>
<td>0.39</td>
<td>0.93</td>
</tr>
<tr>
<td>MVPA*</td>
<td>≥ 562.50</td>
<td>0.34</td>
<td>0.90</td>
<td>0.67</td>
<td>0.37</td>
<td>0.77</td>
<td>0.60</td>
</tr>
<tr>
<td>LPA**</td>
<td>178.50-562.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note: Cut-point determined for lowest d² given a specificity ≥ 0.90

**Note: Cut-points for LPA are the boundaries for SB and MVPA

Table 2. Inter-rater reliability of the MotionWatch8

<table>
<thead>
<tr>
<th>Watch</th>
<th>N</th>
<th>Mean CPM (SD)</th>
<th>Pearson Correlation</th>
<th>ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watch 1</td>
<td>1217</td>
<td>321.44 (316.52)</td>
<td>0.981*</td>
<td>0.979 (0.977, 0.981)*</td>
</tr>
<tr>
<td>Watch 2</td>
<td>1217</td>
<td>276.84 (295.72)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p<0.01

Table 3. Interclass reliability of the MotionWatch8 for measuring sedentary behaviour, light physical activity, and moderate physical activity over 14 days

<table>
<thead>
<tr>
<th>Activity Level</th>
<th>1 Day (95% CI)</th>
<th>4 Days (95% CI)</th>
<th>7 Days (95% CI)</th>
<th>10 Days (95% CI)</th>
<th>14 Days (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB</td>
<td>0.76 (0.66, 0.84)</td>
<td>0.91 (0.87, 0.94)</td>
<td>0.95 (0.93, 0.96)</td>
<td>0.96 (0.94, 0.97)</td>
<td>0.98 (0.96, 0.99)</td>
</tr>
<tr>
<td>LPA</td>
<td>0.69 (0.57, 0.78)</td>
<td>0.89 (0.84, 0.92)</td>
<td>0.93 (0.91, 0.95)</td>
<td>0.95 (0.93, 0.96)</td>
<td>0.97 (0.95, 0.98)</td>
</tr>
<tr>
<td>MVPA</td>
<td>0.69 (0.56, 0.78)</td>
<td>0.90 (0.86, 0.93)</td>
<td>0.95 (0.93, 0.96)</td>
<td>0.96 (0.95, 0.97)</td>
<td>0.97 (0.96, 0.99)</td>
</tr>
</tbody>
</table>
**Table 4** Interclass reliability of the MotionWatch8 for measuring sleep over 14 days

<table>
<thead>
<tr>
<th>All Participants (N=151)</th>
<th>Intraclass Reliability Coefficients (95% CI)</th>
<th>1 Day</th>
<th>4 Days</th>
<th>7 Days</th>
<th>14 Days</th>
<th>Days of Monitoring Required to Achieve Acceptable Reliabilities of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration</td>
<td></td>
<td>0.46</td>
<td>0.71</td>
<td>0.84</td>
<td>0.92</td>
<td>2.74  4.70  10.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.40, 0.52)</td>
<td>(0.63, 0.78)</td>
<td>(0.80, 0.88)</td>
<td>(0.89, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td></td>
<td>0.55</td>
<td>0.82</td>
<td>0.90</td>
<td>0.94</td>
<td>1.91  3.27  7.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.49, 0.61)</td>
<td>(0.76, 0.86)</td>
<td>(0.87, 0.92)</td>
<td>(0.93, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td></td>
<td>0.63</td>
<td>0.83</td>
<td>0.92</td>
<td>0.96</td>
<td>1.37  2.35  5.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.57, 0.68)</td>
<td>(0.78, 0.87)</td>
<td>(0.90, 0.94)</td>
<td>(0.95, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Sleep Latency</td>
<td></td>
<td>0.33</td>
<td>0.40</td>
<td>0.73</td>
<td>0.86</td>
<td>4.74  8.12  18.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.27, 0.39)</td>
<td>(0.23, 0.55)</td>
<td>(0.66, 0.79)</td>
<td>(0.83, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td></td>
<td>0.64</td>
<td>0.85</td>
<td>0.93</td>
<td>0.96</td>
<td>1.31  2.25  5.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.59, 0.70)</td>
<td>(0.81, 0.89)</td>
<td>(0.91, 0.94)</td>
<td>(0.95, 0.97)</td>
<td></td>
</tr>
</tbody>
</table>
Appendix C: Description of cognitive measures included in Alzheimer’s Disease

Assessment Scale Cognitive Plus score

Alzheimer’s Disease Assessment Scale

The Alzheimer’s Disease Assessment Scale consists of 11 brief cognitive tests assessing memory, language, and praxis [456]. Scores range from 0 to 70, with higher scores indicating greater severity of cognitive impairment.

Montreal Cognitive Assessment

The Montreal Cognitive Assessment consists of 30 brief questions assessing memory, language, praxis, and executive function [457]. Scores range from 0 to 30, with higher scores indicating better cognitive performance.

Trail Making Test A and B

Trail Making Test A and B is a measure of executive function, specifically set-shifting [458]. Trail Making Test A requires the participant to draw lines that connect encircled numbers sequentially, such as drawing a line from 1 to 2, 2 to 3, and 3 to 4. Trail Making Test B consists of encircled numbers and letters. Participants were instructed to draw a line as quickly and as accurately as possible from 1 to A, A to 2, 2 to B, B to 3, and so on, until they completed the task. We recorded the amount of time (in seconds) it took to complete each task, and calculated the difference score between part B and part A. Smaller difference scores indicate better cognitive performance.
Digit Span Forward and Backward

The Digit Span Forward and Backward is a measure of executive function, which examines working memory [459]. The test consists of 7 pairs of random number sequences that the assessor reads aloud at the rate of 1 per second. The sequence begins with 3 digits and increases by 1 at a time up to a length of 9 digits. The test includes 2 sequences of each length and testing ceases when the participant fails to recollect any 2 with the same length. The score recorded, ranging from 0 to 14, is the number of successful sequences. For digit span forward, the participant's task is to repeat each sequence exactly as it is given. For digit span backward, the participant's task is to repeat each sequence in reverse order. The difference between the verbal digit span forward and backward test scores is used, with smaller difference scores indicating better working memory.

Animal and Vegetable Fluency

Both animal and vegetable fluency are tests of verbal fluency [459]. For each test, participants were asked to name as many objects which fit the category (i.e., animals or vegetables) as they could within 1 minute. Higher scores indicated better language skills.

Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) is a measure of executive function and information processing [458]. The tests consists of a series of numbers (1-9) and corresponding symbols. Participants are requested to draw the correct symbols for given digits during a 90 second time period. Higher scores indicate better executive function and information processing.
Appendix D: Code used for analyses (Python, R, FreeSurfer, and Excel Macros) and results of analytical models in Chapters 3-7

Most of the analyses performed in this thesis were conducted in R version 3.5.1. The statistical analyses in Chapter 3 were originally conducted in SPSS 22.0; however, I have re-conducted these analyses in R version 3.5.1 for simplicity and reproducibility. Several of the outcome variables in Chapters 3 and 4 used an Excel Macro and Chapter 3 also created outcome variables using Python. Chapter 5 analyses were conducted in FreeSurfer v 6.0.

In order to promote open science, I have created a repository online at GitHub which contains the complete statistical output. All results and statistical code are posted for Chapters 3-7. The link can be found here:

https://github.com/ryanfalck/Appendix-D-RSF-PhD-Thesis/tree/Analyses-by-thesis CHAPTER

Content is separated by chapter. More information or questions can be directed to ryan.falck@hiphealth.ca
## Appendix E: Model fit statistics for structural equation models in Chapter 4

<table>
<thead>
<tr>
<th>Model</th>
<th>$\chi^2 (df)$</th>
<th>CFI</th>
<th>RMSEA</th>
<th>SRMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>387.30 (167)</td>
<td>0.896</td>
<td>0.098</td>
<td>0.057</td>
</tr>
<tr>
<td>Sleep Fragmentation</td>
<td>760.61 (496)</td>
<td>0.914</td>
<td>0.062</td>
<td>0.071</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>821.84 (496)</td>
<td>0.906</td>
<td>0.069</td>
<td>0.073</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>812.72 (471)</td>
<td>0.887</td>
<td>0.073</td>
<td>0.065</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>836.70 (496)</td>
<td>0.858</td>
<td>0.071</td>
<td>0.073</td>
</tr>
</tbody>
</table>

*Note: CFI= Comparative Fit Index; RMSEA= Root Mean Square Error Approximation; SRMR= Standardized Root Mean Square Residual*
Appendix F: Description of compliance measures in Chapter 7

Consensus Sleep Diary Compliance
We tallied the number of days wherein the participant had completed entries in the consensus sleep diary (CSD) for both time they went to sleep (“What time did you try to go to sleep?”), and the time they got out of bed the next morning (“What time did you get out of bed for the day?”). Participants were considered compliant for that day if they had completed both entries. We then calculated the percent compliance to the CSD protocol over 14 days monitoring at baseline, 12 weeks, and 24 weeks follow-up. Participants completed 89% of all CSD entries across all three time points (Baseline= 91%; 12 weeks= 85%; 24 weeks= 90%).

MotionWatch8 Protocol Compliance
We determined compliance to the MotionWatch8 (MW8) protocol based on whether the participant had a completed CSD entry and corresponding MW8 event marker time stamp (i.e., within 1 hour of corresponding CSD entry) for 1) the time the participant started trying to sleep and 2) the time the participant got out of bed in the morning. We then tallied the number of compliant evenings and mornings wherein the participant had completed both the CSD and MW8 protocol, and then calculated the percent compliance over 14 days monitoring at baseline, 12 weeks, and 24 weeks follow-up. There was an average compliance to our MW8 protocol of 71% over the course of the intervention (Baseline= 67%; 12 weeks= 73%; 24 weeks= 72%).

Bright Light Therapy Prescription Compliance
Participants in the multimodal personalized chronotherapy (INT) group received monthly calendars which they were asked to complete and return to us by mail. These calendars asked
participants to log whether they completed their BLT prescription for both the morning and evening for each day of the month. We then calculated compliance to the BLT program for both morning and evening BLT.

Participants completed and returned 91% of their monthly calendars. Average participant adherence to the BLT prescription over the 20-week BLT prescription was 62% to the morning BLT dose, and 68% to the evening BLT dose. Compliance decreased for the morning dose of BLT from 76% during the first month of BLT (i.e., weeks 5-8) to 63% during the last month (weeks 21-24); compliance decreased for the evening dose of BLT from 68% during the first month of BLT to 58% during the last month.

Physical Activity Promotion Program Adherence

Weekly physical activity (PA) was monitored for INT participants using the Fitbit online Dashboard over the course of the 20-week PA promotion program. We calculated adherence to the PA promotion program as the proportion of average minutes/week of PA recorded in the 2 weeks prior to each bi-weekly follow-up phone call versus the participants PA goal for those 2 weeks. For example, we calculated adherence to the PA promotion program at the first follow-up phone call (i.e., Week 6 of the 24 week intervention) as the proportion average minutes/week of PA recorded by the Fitbit during Weeks 5 and 6 versus the participant’s PA goal during Week 5 and 6. Participants were considered to be 100% adherent to their PA goal if they met or exceeded their PA goal during the previous two weeks. For example, if a participant averaged 200 minutes/week of PA and had a goal of 150 minutes/week of PA, then they were considered to be 100% adherent during the corresponding time point.
Average participant adherence to the PA prescription over the 20-week counselling program was 73%. During the first follow-up phone call (Week 6), 66% of participants were meeting their PA goals. During the last follow-up phone call (Week 24), 71% of participants were meeting their PA goals.
Appendix G: Differences in sleep and intraclass reliability coefficients of the
MotionWatch8 for older adults with and without Mild Cognitive Impairment

Table 1. Differences in participant characteristics by Mild Cognitive Impairment status

<table>
<thead>
<tr>
<th>Participant Characteristic</th>
<th>All Participants (N= 151)</th>
<th>Older Adults without Mild Cognitive Impairment (N= 69)</th>
<th>Older Adults with Mild Cognitive Impairment (N= 82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.19 (7.26)</td>
<td>69.42 (6.36)</td>
<td>72.67 (7.66)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>%Female</td>
<td>66.89 %</td>
<td>76.81%</td>
<td>58.54%</td>
<td>0.03</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26.71 (5.05)</td>
<td>25.91 (5.16)</td>
<td>27.45 (4.87)</td>
<td>0.13</td>
</tr>
<tr>
<td>%Retired</td>
<td>77.48%</td>
<td>78.26%</td>
<td>76.83%</td>
<td>0.99</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>4.64%</td>
<td>1.45%</td>
<td>7.32%</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>13.91%</td>
<td>14.49%</td>
<td>13.41%</td>
<td>0.26</td>
</tr>
<tr>
<td>Trade school</td>
<td>11.26%</td>
<td>7.25%</td>
<td>14.63%</td>
<td></td>
</tr>
<tr>
<td>Some university</td>
<td>15.89 %</td>
<td>14.49%</td>
<td>17.07%</td>
<td></td>
</tr>
<tr>
<td>University degree or higher</td>
<td>54.30%</td>
<td>62.32%</td>
<td>47.56%</td>
<td></td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>1.32%</td>
<td>1.45%</td>
<td>1.22%</td>
<td></td>
</tr>
<tr>
<td>Past Smoker</td>
<td>49.67%</td>
<td>50.72%</td>
<td>48.78%</td>
<td>0.96</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>49.01%</td>
<td>47.83%</td>
<td>50.00%</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>26.49%</td>
<td>17.39%</td>
<td>34.15%</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17.22%</td>
<td>13.04%</td>
<td>20.73%</td>
<td>0.30</td>
</tr>
<tr>
<td>Arthritis</td>
<td>13.25%</td>
<td>13.04%</td>
<td>13.41%</td>
<td>0.99</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>7.95%</td>
<td>10.14%</td>
<td>6.10%</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.89%</td>
<td>20.23%</td>
<td>12.20%</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>16.56%</td>
<td>7.25%</td>
<td>24.39%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2.65%</td>
<td>1.45%</td>
<td>3.66%</td>
<td>0.74</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.99%</td>
<td>0.00%</td>
<td>3.66%</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of Medications</td>
<td>2.27 (2.15)</td>
<td>2.01 (1.75)</td>
<td>2.49 (2.43)</td>
<td>0.17</td>
</tr>
<tr>
<td>Sleeping Medication Use</td>
<td>13.25%</td>
<td>17.39%</td>
<td>9.76%</td>
<td>0.26</td>
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<tr>
<td>Diagnosed Obstructive Sleep Apnea</td>
<td>3.57%</td>
<td>0.00%</td>
<td>7.17%</td>
<td>0.99</td>
</tr>
<tr>
<td>CPAP1 Use</td>
<td>3.57%</td>
<td>0.00%</td>
<td>7.17%</td>
<td>0.99</td>
</tr>
<tr>
<td>MMSE2 Score</td>
<td>28.89 (1.11)</td>
<td>29.22 (0.87)</td>
<td>28.61 (1.21)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MoCA3 Score</td>
<td>24.79 (2.83)</td>
<td>27.19 (1.10)</td>
<td>22.77 (2.19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>7.28 (4.00)</td>
<td>6.62 (5.44)*</td>
<td>7.47 (4.71)*</td>
<td>0.15*</td>
</tr>
<tr>
<td>Subjective Sleep Duration (min/day)</td>
<td>373.60 (73.43)</td>
<td>393.89 (111.30)*</td>
<td>363.23 (96.99)*</td>
<td>0.01*</td>
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<tr>
<td>Pittsburgh Sleep Quality Index Measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Duration (min/day)</td>
<td>401.10 (51.23)</td>
<td>415.75 (79.05)*</td>
<td>390.18 (68.87)*</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Fragmentation Index</td>
<td>31.17 (11.03)</td>
<td>30.51 (16.68)*</td>
<td>32.71 (14.76)*</td>
<td>0.23*</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>82.57 (6.10)</td>
<td>82.95 (9.06)*</td>
<td>82.05 (8.52)*</td>
<td>0.40*</td>
</tr>
<tr>
<td>Sleep Latency (min/day)</td>
<td>6.72 (9.00)</td>
<td>6.14 (13.70)*</td>
<td>7.35 (11.88)*</td>
<td>0.41*</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min/day)</td>
<td>85.70 (34.43)</td>
<td>84.92 (53.52)*</td>
<td>87.78 (47.40)*</td>
<td>0.63*</td>
</tr>
</tbody>
</table>

1Continuous Positive Air Pressure Machine
2Mini Mental State Exam
3Montreal Cognitive Assessment

*Controlling for age, sex, sleep medication use
<table>
<thead>
<tr>
<th>Table 2. Reliability coefficients</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
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<tr>
<td>All Participants (N= 151)</td>
</tr>
<tr>
<td>Sleep Duration</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Fragmentation Index</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sleep Latency</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Older Adults without Mild Cognitive Impairment (N= 69)</td>
</tr>
<tr>
<td>Sleep Duration</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Fragmentation Index</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Sleep Latency</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Older Adults with Mild Cognitive Impairment (N= 82)</td>
</tr>
<tr>
<td>Sleep Duration</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Fragmentation Index</td>
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<tr>
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</tr>
<tr>
<td>Sleep Efficiency</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Sleep Latency</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Appendix H: Chapter 4 post-hoc analyses examining the independent relationships of sedentary behaviour and sleep quality with older adult cognitive function

<table>
<thead>
<tr>
<th>Predictors of Physical Activity</th>
<th>Model 1 Pittsburgh Sleep Quality Index</th>
<th>Model 2 Sleep Fragmentation</th>
<th>Model 3 Sleep Efficiency</th>
<th>Model 4 Sleep Duration</th>
<th>Model 5 Sleep Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.26 ± 0.13*</td>
<td>0.21 ± 0.13</td>
<td>0.21 ± 0.13</td>
<td>0.20 ± 0.13</td>
<td>0.21 ± 0.13</td>
</tr>
<tr>
<td>Sex</td>
<td>5.66 ± 2.00**</td>
<td>5.61 ± 2.00**</td>
<td>5.60 ± 2.00**</td>
<td>5.60 ± 2.00**</td>
<td>5.61 ± 2.00**</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>3.06 ± 1.75</td>
<td>3.11 ± 1.75</td>
<td>3.11 ± 1.75</td>
<td>3.11 ± 1.75</td>
<td>3.11 ± 1.75</td>
</tr>
<tr>
<td>Use of Sleeping Medications</td>
<td>-4.61 ± 2.81</td>
<td>-4.75 ± 2.81</td>
<td>-4.75 ± 2.81</td>
<td>4.75 ± 2.81</td>
<td>4.74 ± 2.81</td>
</tr>
</tbody>
</table>

| Predictors of Sleep Quality     |                                      |                             |                          |                        |                      |
| Age                             | 0.09 ± 0.01**                        | 0.36 ± 0.09**               | -0.05 ± 0.05             | 0.02 ± 0.01*          | 0.01 ± 0.05          |
| Sex                             | -1.11 ± 0.66                         | -1.80 ± 1.42                | 1.58 ± 0.76*             | 0.02 ± 0.14           | -1.36 ± 0.81         |
| Smoking Status                  | 0.44 ± 0.57                          | 1.31 ± 1.20                 | 1.30 ± 0.65*             | 0.20 ± 0.12           | -0.51 ± 0.68         |
| Use of Sleeping Medications     | 5.63 ± 0.93**                        | -0.50 ± 1.93                | -0.56 ± 1.03             | 0.17 ± 0.20           | 2.26 ± 1.10*         |
| Average Number of Awakenings    | 0.91 ± 0.10**                        | -0.47 ± 0.05**              |                          |                        | 0.16 ± 0.06**        |

Relationships of Sedentary Behaviour and Sleep Quality with ADAS-Cog Plus

<table>
<thead>
<tr>
<th></th>
<th>Model 1 Pittsburgh Sleep Quality Index</th>
<th>Model 2 Sleep Fragmentation</th>
<th>Model 3 Sleep Efficiency</th>
<th>Model 4 Sleep Duration</th>
<th>Model 5 Sleep Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary Behaviour</td>
<td>0.00 ± 0.01</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.01</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>0.00 ± 0.01</td>
<td>-0.01 ± 0.01</td>
<td>-0.02 ± 0.01**</td>
<td>0.11 ± 0.06</td>
<td>0.02 ± 0.02</td>
</tr>
</tbody>
</table>

Covariance between Sedentary Behaviour and Sleep Quality

<table>
<thead>
<tr>
<th></th>
<th>Model 1 Pittsburgh Sleep Quality Index</th>
<th>Model 2 Sleep Fragmentation</th>
<th>Model 3 Sleep Efficiency</th>
<th>Model 4 Sleep Duration</th>
<th>Model 5 Sleep Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.53 ± 3.28</td>
<td>7.91 ± 6.75</td>
<td>6.68 ± 3.65</td>
<td>0.09 ± 0.70</td>
<td>2.84 ± 3.83</td>
</tr>
</tbody>
</table>

Note: ADAS-Cog Plus= Alzheimer’s Disease Assessment Scale Plus

*p < 0.05; **p < 0.01; aAdjusted for number of awakenings each night